# Committee for Risk Assessment (RAC)

# Committee for Socio-economic Analysis (SEAC)

## Opinion on an Application for Authorisation for

## Diarsenic trioxide

## Industrial use of diarsenic trioxide as processing aid in gold electroplating

**ECHA/RAC/SEAC: (AFA-O-0000004619-65-12/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:

**Industrial use of diarsenic trioxide as processing aid in gold electroplating**

Intrinsic property referred to in Annex XIV:

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

Applicant

**Linxens France**

Reference number

**11-0000000334-83-0001**

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***.

## ADOPTION 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:

**Industrial use of diarsenic trioxide as processing aid in gold electroplating**

## 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.

## JUSTIFICATIONS

| | |
|---|---|
| **Substance name:** | Diarsenic trioxide |
| **Name of applicant(s):** | Linxens France |
| **Submission number:** | DK004379-42 |
| **Use name:** | Industrial use of diarsenic trioxide as processing aid in gold electroplating |
| **Reference number:** | 11-0000000334-83-0001 |

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/$m^3$ 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:

**„Industrial use of diarsenic trioxide as a processing aid in gold electroplating“**

This scenario covers all activities associated with the use of diarsenic trioxide as a processing aid in the gold electroplating process including mixing of the formulation and transfer.

The exposure of workers includes the following:

WCS1: Mixing of the formulation containing the substance into a large container (PROC 5)
WCS2: Calendering operations (PROC 6)
WCS3: Transfer of the formulation to large containers at dedicated facilities (PROC 8b)
WCS4: Transfer of the substance (in preparation) into small containers for analytical verification of the concentration (PROC 9)
WCS5: Potentially closed processing operations with minerals/metals at elevated temperature (PROC22)

According to the information provided by the applicant in response to a request

for additional information, WCS 2, 4 and 5 do not take longer than 5 minutes each. The duration of WCS 3 is described as “a few minutes” and it is stated that there is no opportunity for exposure in WCS 1 because the actual mixing of the stock solution is fully automated and enclosed.

The substance is used six days per week. The maximum amount of diarsenic trioxide used is 50 kg per annum, corresponding to 167 gram per day.

The conditions of use may be generally characterised as well controlled. Biomonitoring data do not contradict this statement.

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

The results of the workplace monitoring indicate that the workers exposure is below **0.3 µg/m³** (personal sampling and stationary measurements).

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

Due to the small quantity of diarsenic trioxide used (50 kg/year, less than 0.2 kg per day), none of the existing modelling tools is fully reliable to estimate dermal exposure. However, there is a need for a starting point in order to do a risk assessment.

The dermal exposure of each scenario is based on modelling using the tool „ECETOC-TRA version 3“.

The exposure values obtained are:
0.014 mg/kg bw/day for WCS1, WCS3 and WCS5,
0.027 mg/kg bw/day for WCS2,
0.034 mg/kg bw/day for WCS4.

These values are considered to represent an overestimation of actual exposures, based on the following reasons:

- The daily use of diarsenic trioxide is less than 200 gram.
- The concentration of diarsenic trioxide in the formulation in this stage is lower than in use 1 (resulting in exposure = 0.11 µg/kg bw/day) because before using it in the plating process it is further diluted (WCS1).
- The duration of the tasks, as indicated in the exposure scenarios, is an overestimation of the actual periods during which there is potential for exposure.
- The dermal exposure is likely to be an overestimate due to the conservatism of the modelling tool used (ECETOC-TRA) which is designed primarily for industrial uses where the quantity of the substance used is significantly larger than in the use applied for here.

As a starting point for the dermal assessment, RAC used the exposure

estimate of WCS 5 (= 14 µg/kg bw/day) because the applicant did not provide any recalculations taking into account the exact durations of the tasks for use 2 and this scenario is the only one which takes place during the whole working day. But it has to be pointed out that usually the duration of the potential dermal exposure during this scenario and during the other four WCSs in use 2 is less than 5 minutes every shift, according to the applicant's response to a request for additional information.

Due to the reasons mentioned above the value of 14 µg/kg bw/day is considered to represent a significant overestimation.

Indirect exposure of human via the environment:

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 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 below0.3 µg/$m^3$.

The quantity of diarsenic trioxide used per annum is 50 kg at the maximum.

RAC agrees with the applicant´s opinion that the indirect exposure of human via the environment can be considered as negligible.

**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 an 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 x $10^{-4}$ per µg As/$m^3$** for the inhalable particulate fraction (based on a 40 year working life) and **6.4 x $10^{-6}$ per µg As/kg bw/day** for the dermal route (based on a 40 years working life). The risk level for general population according to RAC dose-response relationship (1.7 x $10^{-5}$) 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 x $10^{-6}$ for workers.

Based on the exposure data described above the excess lung cancer risk via the inhalation route is therefore about 0.3 x 1.4 x $10^{-4}$ = **4.2 x $10^{-5}$** (40 years exposure) and 14 x 6.4 x $10^{-6}$ = **9.0 x $10^{-5}$** 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 100 workers caused by exposure of 40 years is 100 x 4.2 x $10^{-5}$ = **4.2 x $10^{-3}$** (inhalation route) and 100 x 9.0 x $10^{-5}$ = **9.0 x $10^{-3}$** (dermal route).

The RMMs described in the application are considered to be appropriate by RAC in reducing the exposures and the risk (local exhaust ventilation, 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

☒ 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

☒ 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

☒ NO

Justification:

The analysis of alternatives undertaken by the applicant sets out the possible alternatives that might be considered for replacing diarsenic trioxide. The applicant reaches the conclusion that it would not be possible to replace their use of diarsenic trioxide by the sunset date with an alternative that was technically and economically feasible.

SEAC concurs with this conclusion based on its assessment of the applicant's analysis. The applicant has investigated a number of alternatives since the initial candidate listing and prioritisation of diarsenic trioxide as an SVHC. The search for an alternative has been undertaken in the context of the apparent proprietary nature of the applicant's process, and the fact that no drop-in alternatives exist, such that all alternatives would need at least partial development to suit the specific needs of the applicant. The technical feasibility of alternatives was assessed by the applicant in terms of the suitability of alternatives in relation to three related technological constraints: Process limitations; the quality of finished products; and market related constraints. The economic feasibility of alternatives was assessed by the applicant primarily in terms of the increased resource use associated with use of the alternatives, and in some cases on the impact on production volume and the need for machine/equipment replacement/modification.

Based on the information made available by the applicant, SEAC is able to

accept that at the present time most of the alternatives considered appear to impose unacceptable quality/performance degradation of the product and/or production capability. In the other cases, the technical feasibility of the alternative has either not been assessed by the applicant given a lack of suitability on safety and risk reduction grounds, or development and testing is currently ongoing and there is not yet enough data to allow the technical validity of the alternative to be fully determined. Although there appears to be promising prospects for successful replacement in some cases, the applicant maintains that the ongoing development, testing and customer proofing required is such that no breakthrough is imminent. SEAC can see no reason to question the applicant's conclusions in this respect, such that SEAC accepts that there are no technically feasible options at the present time.

Regarding economic feasibility, the applicant asserts that in the case of nearly all the alternatives considered there would need to be an increase in the amount of gold used in order to obtain the same coating level and quality of product (aside from any other technical feasibility issues) as under the current process using diarsenic trioxide. Specifically, an increase of 15-20% more gold is considered necessary to come close to the current technical requirements that would match the current competitive advantage enjoyed by the applicant using the arsenic process. This increase in gold use is estimated by the applicant to increase costs by around €4-7 million per year. Although the precise monetary amount stated by the applicant seems to vary in the application (for reasons unknown to SEAC), it has been possible for SEAC to verify that the order of magnitude is correct based on the limited information available on volume and price of gold as indicated by the applicant. In some cases, the applicant suggests there are also additional costs associated with reduced production capacity and/or modifications/replacement of equipment/machinery depending on the alternative being considered, though no quantitative monetary estimate of this cost has been given in the economic feasibility assessment. In a few of the alternatives considered, economic feasibility has not been assessed, since those alternatives were found to be technically infeasible or still under development/testing for their technical suitability. Whilst SEAC has some reservations concerning the lack of detail in assessing the increased cost of using alternatives, SEAC has nevertheless been able to confirm that the assessment of economic feasibility indicates the lack of a suitable alternative.

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

☒ YES

☐ NO

Justification:

The applicant describes the technical and economic feasibility of eleven

selected alternatives. The search for alternatives began once the applicant learned of the candidate listing and prioritisation of diarsenic trioxide as an SVHC. Given their focus on process adaptation and modification for production purposes and hence a lack of relevant experience in primary materials research, the applicant has primarily relied on consultation and contact with manufacturers of potential alternatives to arrive at their final list of possible alternatives that have been examined in the analysis of alternatives. The applicant believes that no supplier of possible alternatives was omitted from the list of those they consulted. Moreover no further suggestions for possible alternatives have been suggested by the ECHA public consultation.

The assessment of technical and economic feasibility describes the nature of the technical and economic feasibility issues arising with each alternative as compared with the current production using diarsenic trioxide. The level of detail provided by the applicant on the nature of the technical feasibility issues varies across the alternatives, and in some cases one has to accept at face value some of the technical issues which the applicant claims are problematic. At the same time, it is clear that further development and testing of alternatives is necessary in other cases, and the applicant has clearly indicated their commitment to continue with this. Despite the lack of detail in some cases then, on balance SEAC considers the description of technical and economic feasibility to adequately describe the current status of the substitution possibilities available to the applicant.

SEAC notes that no investigation has been undertaken by the applicant to assess any potential alternative technologies/process that would make redundant the process (as distinct from the substance) under which diarsenic trioxide is used. Whilst it is therefore unclear the extent to which such alternative technologies/process may be available, it is clear from the analysis that the process employed by the applicant provides the basis of its technological and commercial advantages over any alternatives. As such, and given the ongoing development and testing towards a substance based alternative, SEAC agrees that the approach taken to assessing alternatives is proportionate and acceptable for the purpose considered.

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

☐ YES

☐ NO

☒ NO SUITABLE ALTERNATIVES EXIST

Justification:

Although a number of the alternatives considered by the applicant are believed by the applicant to be available in sufficient quantities for their use, as discussed in section 7.2, SEAC agrees that the alternatives are not technically and economically feasible, and hence they cannot be considered suitable.

According to the applicant, there are promising, albeit very uncertain prospects for successful replacement by some of the alternatives considered. Further development and testing of 5 of the alternatives is warranted according to the applicant. In all cases there is uncertainty as to whether the alternative will work, pending further investigation and testing. Moreover the time period indicated by the applicant to be necessary to develop the alternatives into viable solutions is at best 3 years and in most cases at least 5 years for introduction of the alternatives into the production process. The availability of some of these technically promising alternatives is unknown at present, given that they are custom made by the suppliers.

**8. For non-threshold substances, have the benefits of continued use been adequately demonstrated to exceed the risks of continued use?**

☒ YES

☐ NO

☐ NOT RELEVANT

Justification:

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. Given the asymmetrical time profile used in the estimation of the cancer burden and the investment and operative costs associated with "non-use", this reduces the transparency of the estimation of impact. However, use of annualised figures is acceptable in that it makes it easier to compare impacts across the different authorisation review periods that can be granted. 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.

*Costs*

The analysis of the costs of "non-use" is based on data from the assessment of alternatives. The available information indicates that although there are a number of possible alternatives (albeit all currently unsuitable), these would

all result in a loss of technical performance (production efficiency) of around 15-20%, as well as an increase of around 15-20% in the quantity of gold required in the manufacturing process in order to achieve an equivalent level of product quality (and hence competitive advantage) as with the diarsenic trioxide process. The costs associated with these two effects have been estimated in terms of the increase in investment costs and operative costs for the "non-use" scenario. The investment costs include the costs of additional capital and infrastructure required to compensate for the reduction in production efficiency, whilst the operative costs consist primarily of the additional costs of gold consumed. Accepting at face value the applicant's estimate of the increase in gold volume required under the "non-use" scenario, the operative costs are transparent to assess, since the price of gold is publicly available. Although it has been difficult to properly scrutinise the evidence on investment costs, it does not seem to be a significant drawback, since it is clear that the main cost driver under the "non-use" scenario is the increase in operative costs (93% of the total increase in annual costs). It should be noted, that given the applicants assessment that none of the alternatives are currently suitable, there would most likely be additional costs under the "non-use" scenario, associated with the temporary suspension of production until an alternative could be brought on stream. The applicant has not included these costs in their benefit-cost comparison, even though they are potentially very significant. As such, SEAC confirms that the cost assessment undertaken by the applicant provides a proportionate analysis and a methodologically and empirically appropriate order of magnitude estimate of the costs of "non-use" of diarsenic trioxide. The costs of "non-use" are estimated by the applicant at €4,654,258 per annum.

*Benefits*

The quantitative analysis of the benefits associated with the "non-use" of diarsenic trioxide is based on a health impact assessment using an 'impact pathway' type methodology. This estimates the change in physical health impacts due to changes in exposures as a result of the "non-use" scenario. The approach is based on linking quantitative relationships between exposure and the health impact of interest. This general procedure is widely used for the assessment of benefits related to pollutants and is considered to be an appropriate methodological approach. The sole health endpoint considered in the quantitative health impact assessment is the number of lung cancer cases. Although the applicant estimated an additional 0.0028 cases of lung cancer for the total exposure time period of 40 years, according to RAC's opinion the exposure levels were incorrectly estimated and the assessment did not consider all relevant exposure routes. As such, RAC re-estimated the additional number of lung cancer cases at $7.0 \times 10^{-5}$ (inhalation route) and $1.2 \times 10^{-6}$ (dermal route) for use 1 (formulation), and $4.2 \times 10^{-3}$ (inhalation route) and $9.0 \times 10^{-3}$ (dermal route) for use 2 (industrial use of diarsenic trioxide). The latter estimate on dermal route was considered by RAC to be a significant overestimate. Concerning the estimation of economic welfare losses associated with this number of excess lung cancer cases, three components are included

in the analysis including: Direct medical treatment costs; productivity losses; and the welfare loss from mortality and morbidity. The specific assumptions and studies used to derive the values for each of these components have been specified, such that the derivation of the total economic burden of lung cancer cases associated with the use of diarsenic trioxide (and hence the benefit of "non-use) is clear and transparent. SEAC confirms that despite some relatively minor issues with the approach taken (for example, whether the implicit assumption of a linear relationship between risk and years of exposure is correct; whether gross or net output is the appropriate measure of productivity loss; and the failure to apply any discounting of take into account the latency of cancer), the methodology, assumptions and studies used are in general appropriate and proportionate. Although the issues mentioned above give rise to some uncertainties concerning the robustness of the ("non-use" scenario) benefits derived, the tendency is that the estimates are likely to be at the conservative (overestimated) end of the spectrum. The benefits of "non-use" are estimated by the applicant at €121 per annum. Although this does not take into account the updated cancer estimates by RAC (including dermal exposures and associated conservatism in risk modelling), SEAC nevertheless has concluded that there is no change in the outcome of the assessment, since the benefit estimates are still negligible under the RAC generated estimates of risk.

*Comparison of benefits and risks of continued use*

Overall, 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. Again, 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:

In identifying the proposed review period, SEAC took note of the following considerations:

- The very small level of risk associated with the continued use (and corresponding negligible benefits of "non-use") of diarsenic trioxide by the applicant;

- The applicant has been proactive in seeking to develop an alternative and there appear to be promising prospects for successful replacement, although no breakthrough is imminent. Nevertheless the applicant appears to be committed to further development, testing and eventual replacement of diarsenic trioxide.

- The applicant did not fully clarify the time required to confirm the technical feasibility and implement one of the potential alternatives. At best a period of 3 years and more likely a period of at least 5 years is mentioned in some parts of the dossier;

- The analysis of alternatives and the assessment of costs indicate that irrespective of the alternative chosen, it is likely there will be significant and perpetual costs associated with "non-use" arising from the need to increase gold consumption by around 15-20% per annum.

Taking into account all of these points, and given that the applicant provided information that they were working towards an alternative potentially being able to be implemented in a period not less than 5 years hence, SEAC recommends a “normal” review period of **seven (7) years.**