

Our Ref:

Your Ref:

Date: 16/10/2024

Dear Sirs/Madams,

**Contract Ref: SC210001**

**Contract Title: Toxicological advice on air pollutants**

You are invited to quote for the above in accordance with the enclosed documents.

Instructions on what information we require you to provide is in Section 4 of the following Request for Quotation document.

Your response should be returned to the following email address by 17:30 on 01/12/2024.

Hannah.hodson-jeffery@environment-agency.gov.uk

Please confirm, by email, whether you intend to submit a quote as we may wish to update you with additional information during the quotation period.

If you have any queries, please do not hesitate to contact me.

Yours sincerely

Hannah Hodson-Jeffery

Senior Air Quality Advisor, Chief Regulators Group

E-mail: hannah.hodson-jeffery@environment-agency.gov.uk

Telephone: 07767005691

**The Environment Agency**, Horizon House, Deanery Road, Bristol, BS1 5AH

**Request for Quotation**

**Ref: SC210001**

**Title: Toxicological advice on air pollutants [Review of published Environmental Assessment Levels for a number of Substances, based on updated toxicological information]**

**Section 1**

**Who is the Environment Agency?**

We are an Executive Non-departmental Public Body responsible to the Secretary of State for Environment, Food and Rural Affairs. Our principal aims are to protect and improve the environment, and to promote sustainable development.

Further information on our responsibilities, Corporate Plan and how we are structured can be found on our Website.

<https://www.gov.uk/government/organisations/environment-agency/about>

**What do we spend our money on?**

We are a major procurer of goods and services within the UK, spending circa £600M per annum, our major spend areas are:

* Flood and Coastal Risk Management (design, construction and maintenance)
* ICT and Telecommunications
* Vehicles and Plant
* Environmental Consultancy and Monitoring
* Temporary Staff and Contractors
* Facilities Management, Energy and Utilities
* Flood Management and Water Related Services

**What do we need from our suppliers?**

Suppliers are vital in supporting the delivery of our corporate plan. We aim to support the economy and society whilst delivering more environmental outcomes for every pound we spend. In many areas we are leading the way on environmental and technical developments. It is our role to ensure that suppliers clearly understand our corporate aims and objectives and know that we are committed to delivering the best value most sustainable solutions, taking into account the whole life cost of our procurement decisions. We promote diversity and equality and treat all of our suppliers fairly.

Our procurement strategy may be of interest to you as a potential supplier. It sets out our priorities and key commitments in a range of areas such as delivering our corporate plan, Government policy, supplier management and sustainable procurement:

<https://www.gov.uk/government/organisations/environment-agency/about/procurement#procurement-strategy>

**Government changes and collaboration**

Since 1 April 2013, the Environment Agency is no longer responsible for delivering the environmental priorities of Wales. This is now the remit of Natural Resources Wales (NRW).Further information can be found here:

<http://naturalresources.wales/splash?orig=/>

By bidding for this requirement, you may also be approached by other members of the Defra network, NRW or other government departments that are specifically named in the tender document.

**Further information**

For further information and to see our commitments to Diversity and Equality, please visit our website.

<https://www.gov.uk/government/organisations/environment-agency/about/procurement>

https://www.gov.uk/government/organisations/environment-agency/about/equality-and-diversity

Also, are you up to date on environmental legislation? See links below for further information.

Waste and Environmental Impact - <https://www.gov.uk/browse/business/waste-environment>

Environmental Regulations - <https://www.gov.uk/browse/business/waste-environment/environmental-regulations>’

**Section 2**

**The Customer**

**Summary**

This work is being commissioned by the Monitoring and Assessment team within the Chief Regulator’s Group at the Environment Agency. The Chief Regulator Group is the focus across the Environment Agency for setting the regulatory strategy, standards and assurance framework, working with colleagues to help EA deliver effective regulation. The Monitoring and Assessment Team leads on addressing and minimising air quality issues of our regulated industry.

## Contract Length

It is anticipated that this contract will be awarded to one supplier for a period of 7 months to end no later than 01/04/2025. Prices will remain fixed for the duration of the contract award period. We may at our sole discretion extend this contract to include related or further work. Any extension shall be agreed in advance of any work commencing and may be subject to further competition. Any amendment to contract prices for the extensions are to be by negotiation.

The Environment Agency Conditions of Contract for Research (Appendix C) shall apply to this contract.

This contract shall be managed on behalf of the Agency by[Hannah](mailto:Hannah) Hodson Jeffery,

Hannah.hodson-jeffery@environment-agency.gov.uk

## Contact Details and Timeline

Hannah Hodson-Jeffery will be your contact for any questions linked to the content of the quote pack or the process. Please submit any questions by email and note that both the question and the response will be circulated to all tenderers that have previously confirmed by email their intention to submit a quotation.

Key elements of the process have been reviewed. Anticipated dates for planned activities are below:

|  |  |
| --- | --- |
| **Activity** | **Due Date** |
| Supplier responses for Request for Quote | 01/12/2024 17:30 |
| Evaluation of Request for Quote submissions | 05/12/2024 |
| Award of contract | 10/12/2024 |
| Project/Contract end date | 01/04/2025 |

It should be noted that these timescales and activities may be subject to change.

**Section 3**

## Evaluation Criteria

We will award this contract in line with the most economically advantageous tender (MEAT) as set out in the following award criteria:

* Price – 60%
* Quality – 40%

The following quality criteria are weighted in accordance with the importance and relevance attached to each one.

|  |  |
| --- | --- |
| Experience of reviewing, assessing and summarising mammalian and human toxicology of chemicals | 35% |
| Adequacy of staff resources (including for project management) | 35% |
| Project methodology (including project management oversight) | 10% |
| Ability to deliver a successful project to time and budget | 20% |

The criteria listed above will be assessed on a 0 to 10 basis and will reflect the following judgements:

|  |  |
| --- | --- |
| **Rating of Response**  **The tenderer provides a response which in the opinion of the evaluators is:** | **Score** |
| **Excellent:** Addresses all of the requirements and provides a response with relevant supporting information which does not contain any weaknesses, giving the Agency complete confidence that the requirements will be met. | 10 |
| **Very Good:** Addresses all of the requirements and provides a response with relevant supporting information, which contains very minor weaknesses, giving the Agency high confidence that the requirements will be met. | 8 |
| **Good:** Addresses all of the requirements and provides a response with relevant supporting information, which contains minor weaknesses, giving the Agency reasonable confidence that the requirements will be met. | 6 |
| **Satisfactory:** Substantially addresses the requirements and provides a response with relevant supporting information which may contain moderate weaknesses, but gives the Agency some confidence that the requirements will be met. | 4 |
| **Weak:** Partially addresses the requirements, or provides supporting information that is of limited relevance or contains significant weaknesses, and therefore gives the Agency low confidence that the requirements will be met. | 2 |
| **Nil:** No response or provides a response that gives the Agency no confidence that the requirements will be met. | 0 |

**Section 4**

**Information to be returned**

**Please note, the following information requested must be provided. Incomplete tender submissions may be discounted.**

Please complete and return the following information:

* details of the personnel you are proposing to carry out the service, including CV’s of your key personnel;
* detail your recent experience of carrying out similar contracts or projects
* details of proposed methodology
* completed Pricing Schedule (Appendix A);
* completed Prior Rights Schedule (Appendix B);
* confirmation that terms and conditions are accepted (Appendix C. Please note that the terms cannot be amended later).

**Section 5**

**Specification**

# Background to the Requirement

The Environment Agency (EA) regulates chemical emissions from industrial and waste management activities under the Environmental Permitting Regulations 2016 (EPR). [Air emissions risk assessment for your environmental permit - GOV.UK (www.gov.uk)](https://www.gov.uk/guidance/air-emissions-risk-assessment-for-your-environmental-permit?msclkid=f8a8695cac2211ecb0599a845ea17d8e) is the principal guidance on environmental risk assessment for new permit applications. Applicants use the online guidance to identify and manage significant emissions that could impact public health and the environment.

In assessing risks to health, the air emissions risk assessment guidance recommends that predicted atmospheric emissions of chemicals released by proposed permit processes are screened against Environmental Assessment Levels (EALs) for the chemicals of concern. EALs have been established by the EA and are defined as air concentrations indicative of non-appreciable or minimal concern to health from short- or long-term inhalation exposure. They cover about 90 substances (see below) including industrial chemicals and classical air pollutants. Many EALs are based on withdrawn occupational exposure limits and were last reviewed in detail in the early 2000s.

The EA published its updated methodology for the derivation of EALs in 2012, with a greater emphasis on a robust review of the scientific evidence on adverse health effects. Working in partnership with Public Health England (PHE), now the UK Health Security Agency, UKHSA, the EA initiated a systematic review of EALs in 2019 to ensure that the existing recommendations are underpinned by the latest science. As a result, the EA has recently completed two rounds of EAL revisions. We have now completed the review of EALs for 23 substances, and developed EALs for several new substances, identified as being critical to the regulation of the carbon capture and storage sector.

**References**

**List of Environmental Assessment Levels**

<https://www.gov.uk/guidance/air-emissions-risk-assessment-for-your-environmental-permit#environmental-standards-for-air-emissions>

**Guidance on the Derivation of Environmental Assessment Levels**

<https://www.gov.uk/government/consultations/derivation-of-new-environmental-assessment-levels-to-air>

**Phase I Consultation on New Environmental Assessment Levels (Nov 2020 to Feb 2021) and Consultation Response Document**

<https://consult.environment-agency.gov.uk/environment-and-business/new-air-environmental-assessment-levels/>

**Review of Environmental Assessment Levels (EALs) for emissions to air: second phase - GOV.UK (www.gov.uk)**

# Specific Objectives/Deliverables

The main objective of this project is to continue the on-going review and revision of EALs by applying the EA 2012 methodology, updated as appropriate to reflect our consultations (see details below). It will include the production of individual dossiers on the toxicology of specific chemicals from the open and grey scientific literature (the dossiers for selenium and piperazine are provided as examples in Appendix D), which will be the basis for establishing updated EALs, short term and/or long-term depending on the data, for each compound. The proposed EALs will be submitted for agreement by the EA and UKHSA. In addition, the contractors may be required to provide expert advice on request, in the form of a briefing note, for selected toxicological issues such as a synthesis of *in vitro* and *in vivo* evidence on genotoxicity and mutagenicity. The work undertaken will be carried out under the direction of the EA’s Chief Scientist’s Group, who will also liaise with UKHSA.

Key activities:

1. Dossiers should be prepared for each individual substance identified in Table 1, which must be consistent with the layout, structure, and content as illustrated in the examples provided. In some cases, the information provided in existing reviews by authoritative bodies may be sufficient to prepare the dossiers. However, where appropriate, additional toxicological studies may be identified and summarised from the published scientific and grey literature. Authoritative bodies include those identified in the updated methodology. (An update to the methodology is in preparation and the draft will be shared with the appointed contractors. While the revised method has not substantially changed the approach, the new guide includes clearer worked examples from recently revised EALs and provides clearer direction on specific aspects such as the choice and value of commonly applied uncertainty factors, however, please see current methodology ([Derivation of new Environmental Assessment Levels to air - GOV.UK (www.gov.uk)](https://www.gov.uk/government/consultations/derivation-of-new-environmental-assessment-levels-to-air)) in the first instance.) but this may be supplemented by other organisations including environmental protection and health agencies in other countries and individual US states.
2. Where available, relevant data and authoritative opinions should be summarised on substance identity and use; absorption, distribution, metabolism, and excretion (ADME); adverse observed effects in human and animal studies from short and long-term exposure, carcinogenicity and genotoxicity, and the derivation of any health-based guidance values reported by authoritative bodies. While the focus should be on the inhalation route, key data from oral studies, which might suggest a more sensitive effect than via inhalation, should also be reported. When referring to studies reported in an existing authoritative review, it is not necessary to review every cited study. However, any study on which a proposed environmental assessment level is based, should be obtained and reviewed, if practical to do so (exceptions being unpublished data and articles only in a foreign language).
3. Each dossier will set out one or more preliminary recommendations for a short- and long-term EAL, as appropriate.  These recommendations can include the adoption of an existing opinion or a new derivation including uncertainty factors, taking account of the updated methodology (available on request).  All approaches must be fully explained including the incorporation of modelling data as appropriate (such as the outcome of benchmark dose modelling) and the justification for use of uncertainty factors.
4. Each dossier should also include an assessment of practical compliance (see the example dossiers provided in Appendix D for further information).
5. After EA internal review, the draft dossiers will be shared with the UK Health Security Agency (UKHSA). They may request further information to clarify the evidence before making final recommendations for an appropriate short- and/or long-term EAL for each substance (if there is sufficient information to do so).  The contractor will be expected to take account of UKHSA feedback before finalising the dossier and any recommendations to ensure a clear narrative.

The list and number of substances to be addressed are listed in Table 1. Where appropriate, we have identified those substances where an initial review was carried out in 2019/20. This text will be shared with the successful contractor. We encourage the tendering contractors to consider the number of these substances that can be reviewed within the available budget, and timescales.

Table 1 Priority Chemicals for EAL review

|  |  |  |  |
| --- | --- | --- | --- |
|  | Substance | CAS No. | Notes |
| 1 | N-Methyl-2-pyrrolidone (NMP) | 872-50-4 |  |
| 2 | Beryllium | 7440-41-7 |  |
| 3 | Aniline | 62-53-3, 142-04-1 (HCl) |  |
| 4 | Bromomethane | 74-83-9 |  |
| 5 | Acetaldehyde | 75-07-0 |  |
| 6 | Nitrogen Monoxide | 10102-43-9 | Initial review available. |
| 7 | Tetrahydrofuran | 109-99-9 |  |
| 8 | Toluene | 108-88-3 |  |
| 9 | Hydrogen Fluoride | 7664-39-3 | Initial review available. |
| 10 | Antimony | 7440-36-0 |  |
| 11 | Ethylene Dibromide | 106-93-4 |  |
| 12 | Carbon Monoxide | 630-08-0 | Initial review available.  Only ST-EAL needed. |
| 13 | Hexane (n) | 110-54-3 |  |
| 14 | Carbon Dioxide (Concentrated) | 124-38-9 |  |
| 15 | Hydrogen Sulphide | 7783-06-4 |  |

Key requirements:

* The supplier will have specialist experience of the synthesis and critical evaluation of mammalian and human toxicology and be able to summarise key studies and decisions effectively and succinctly.
* A single point of contact will be provided by the supplier.
* Deliverables and timescales are outlined below.

### Timescales/Deadlines

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Task No. | Deliverable | Responsible party | Format / Compatibility Requirements | Date of completion, end: |
| 1 | **Start-up meeting** with project team and the EA steering group, confirming:   * Substances for which EALs are to be developed * Approach to EAL development * Project deliverables and timings | Supplier | MS Teams meeting/ Telecon | 20 Dec 2024 |
| 2 | **Draft 1 of dossiers** for agreed chemicals listed in Table 1 to EA (these can be provided in batches, but all drafts must be submitted by the task end date) | Supplier | Word documents | 20 Jan 2024 |
| 3 | EA steering group reviews dossiers and provides **comments** back to project team (can occur in batches)  EA review - to ensure dossiers are suitable for sharing with UKHSA  UKHSA review - (a) feedback requested and (b) final recommendations made | EA project manager | Track changes in word document | 17 Feb 2025 |
| 4 | **Draft 2 of dossiers** for above chemicals for EA 2nd review | Supplier | Word documents | 06 Mar 2025 |
| 5 | **Final Dossiers** to EA  Final review to ensure narrative is clear. | Supplier | Word document | 20 Mar 2025 |
| 6 | **Progress meeting** with project team and the EA steering group, confirming:   * Final prioritisation * Next steps for new dossiers | Supplier | MS Teams meeting/ Telecon | 06 Apr 2025 |

### Skills of Personnel Required

# Technical expertise in mammalian and human toxicology including critical evaluation of primary open and grey literature on a range of industrial contaminants.

# Excellent communication skills (written, pictorial and verbal).

# Ability to work collaboratively and share knowledge.

**Section 6**

**Contract Management**

This contract shall be managed on behalf of the Agency by[Hannah](mailto:Hannah) Hodson-Jeffery (Hannah.hodson-jeffery@environment-agency.gov.uk)

The contractor is required to maintain close liaison with the Environment Agency's Project Manager.

During the course of the project, the contractor will provide the Environment Agency’s Project Manager with regular updates (monthly or fortnightly) regarding:

* progress and difficulties encountered with the project
* any proposed changes to the manner in which the project is run
* time spent on the project
* details of the financial spend during the previous month.

An Environment Agency project steering group will be set up to act as the technical quality review panel for the work and outputs. This panel will include representation from UKHSA, who will provide an authoritative and independent peer review of the documents produced. Working closely with UKHSA is an essential part of this project. The project advisory group will review drafts produced by the contractor, prior to acceptance. You should ensure that sufficient time is allowed within the project to consult with the project steering group in directing the project. Approximately 3 weeks has been built into the schedule to allow review of draft documents.

The contractor should allow enough time for project meetings to discuss progress and agree future scope. There will be two full project meetings, both of which will be virtual and half days (3-4 hours); one at the start-up of the project and one to discuss the progress of the dossiers and agree the work schedule for the remainder of the project. Other project meetings and any other discussions needed, including project closure, will be conducted where necessary. Any additional telephone discussions up to 1 hour will be integral to the project and will not be costed.

We will raise purchase orders to cover the cost of the services and will issue to the awarded supplier following contract award.

Before the invoice is issued, a fee note must be emailed in advance to the contract manager for approval. All invoices must quote the purchase order number in order to be processed. A file copy invoice must be provided to the contract manager, on request. The timescale for payment of invoices will be up to 30 days after we have received a valid invoice.

It is proposed that full payment be made on acceptance of the final dossiers for new substances at the end of March 2025. Alternative programmes of work and payment schedules will be considered.

**Section 7**

**Sustainability Considerations**

We are committed to continually improving our sustainability performance. The Environment Agency has set itself tough objectives as a clear commitment and contribution to sustainable development throughout England. The Agency recognises that this can only be achieved through commitment from all sectors of society and it is intent on raising awareness amongst industry and commerce.

Contractors must adopt a sound proactive environmental approach, designed to minimise harm to the environment.

Environmental criteria should be considered as part of your tender submission with credit given for innovation. Factors to be considered could include areas such as:

* + - Paper use: All documents and reports prepared by consultants and contractors are produced wherever possible in electronic format; alternatively on recycled paper containing at least 100% post-consumer waste and printed double sided.
    - Travel: We will reduce face to face meetings by using email and videoconferencing. Any face to face meetings to be held in locations which will minimise travel and close to public transport links.
    - Packaging: should be kept to a minimum. Re-use and disposal issues must be considered.
    - Efficient Energy and Water Use.
    - Disposal of Waste: Whilst on site the contractor is responsible for the disposal of their own waste and can only use client facilities with express permission from the on-site facilities officer.
    - Whilst on site, contractors should comply with the local environmental policy statement which will be made available to you in advance or on arrival.

**Diversity and Equal Opportunities**

We are committed to promoting equality and diversity in all we do and valuing the diversity of our workforce, customers and communities.  As a public body, we publish regular information about what our equality objectives are and how we’re meeting them.

<https://www.gov.uk/government/organisations/environment-agency/about/equality-and-diversity>

**Health and Safety**

Contractors will be responsible for making sure all required health and safety aspects including risk assessments are undertaken and required management measures are in place to protect worker exposure. This includes management of all partners, consortium members and subcontractors.

**-eMission2030 – The Environment Agency Sustainability Plan**

## Sustainability Objectives

As the Environment Agency, our overarching aim is to protect and improve the environment for people and wildlife. Over the last 10 years we have achieved significant reductions in our environmental impacts that occur through our everyday operations. This included a 40% reduction in our carbon emissions and a 37% reduction in the number of miles we travel.

**Supply chain**

​​​​​​​Sustainable procurement is part of everyday responsible procurement. Two thirds of our impacts are from our suppliers and supply chains. Therefore, we have a great opportunity to reduce negative impacts and enhance the positive impacts of our purchasing activity.

Sustainable procurement is taking into account the whole lifecycle sustainability of the purchase from raw material through to disposal when purchasing goods and services. It is an approach embedded in procurement activity that:

* achieves value for money taking into account whole life costs
* generates benefits to us, society and the economy
* minimises damage to the environment

## Section 8

### Additional Information

### Copyright and confidentiality

Unless otherwise indicated, the copyright of all the documentation belongs to the Environment Agency, and the documentation is to be returned to us with your tender. The contents of the documentation must be held in confidence by you and not disclosed to any third party other than is strictly necessary for the purposes of submitting your quote. You must also ensure that a similar obligation of confidentiality is placed upon any third party to whom you may need to disclose any of the documentation for the purposes of the tender.

### Accuracy of documentation

You should check all documentation; should any part be found to be missing or unclear you should immediately contact us at the address given in the covering letter. No liability will be accepted by the Environment Agency for any omission or errors in the documentation which could have been identified by you.

### Amendments to documentation

Prior to the date for return of tenders, we may clarify, amend or add to the documentation. A copy of each instruction will be issued to every Tenderer and shall form part of the documentation. No amendment shall be made to the documentation unless it is the subject of an instruction. The Tenderer shall promptly acknowledge receipt of such instructions.

### Alternative Offers

Alternative offers may be considered if they constitute a fully priced alternative and are submitted in addition to a quotation complying with the requirements of the Invitation to Quote Documents. If, for any reason you wish to submit an alternative offer without a fully compliant tender please contact us in accordance with the details in the covering letter.

## Continuity of personnel

The Contractor shall employ sufficient staff to ensure that the Services are provided at all times and in all respects to the Project Standard. It shall be the duty of the Contractor to ensure that a sufficient reserve of staff is available to ensure project delivery in the event of staff holidays, sickness or voluntary absence

The Environment Agency will be notified immediately of any changes to personnel associated with the project. The Contractor will ensure that every effort is made to replace outgoing staff with personnel of equal calibre and expertise. All new members of staff undertaking work for the Project will need to be agreed by the Environment Agency prior to commencement.

At all times, the Contractor shall only employ in the execution and superintendence of the Contract persons who are suitable and appropriately skilled and experienced.

## Intellectual property rights

All results, including material and tools produced, developed or paid for under this contract shall be the property of the Environment Agency.

## References

The Environment Agency may request recent and relevant references prior to the award of the project.

**Contract award**

This Request for Quote is issued in good faith but we reserve the right not to award any or all of this work.

### DATA PROTECTION ACT ADDENDUM TO SPECIFICATION

## Protection of personal data

In order to comply with the Data Protection Act 1998 the Contractor must agree to the following:

* You must only process the personal data in strict accordance with instructions from the Environment Agency.
* You must ensure that all the personal data that we disclose to you or you collect on our behalf under this agreement are kept confidential.
* You must take reasonable steps to ensure the reliability of employees who have access to personal data.
* Only employees who may be required to assist in meeting the obligations under this agreement may have access to the personal data.
* Any disclosure of personal data must be made in confidence and extend only so far as that which is specifically necessary for the purposes of this agreement.
* You must ensure that there are appropriate security measures in place to safeguard against any unauthorised access or unlawful processing or accidental loss, destruction or damage or disclosure of the personal data.
* On termination of this agreement, for whatever reason, the personal data must be returned to us promptly and safely, together with all copies in your possession or control.

# APPENDIX A - PRICING SCHEDULE

ALL COSTS QUOTED MUST BE EXCLUSIVE OF VAT

All costs must be quoted on this schedule. Any costs not detailed will not be paid.

Task 7 is for the provision of new dossiers for an undefined number of substances. You should provide a day rate for all staff that may work on a dossier. You should provide sufficient information to enable us to make a comparison of indicative costs for this item on a time and materials basis for a simple dossier (for example, acrylamide or piperazine) and a potentially more complicated dossier (for example, selenium or copper).

Please detail your task costs in the table below.

|  |  |  |  |
| --- | --- | --- | --- |
| **Cost Proposal (To be completed by Supplier)** | | | |
| **Tasks** | **Hourly Rate** | **No of Hours** | **Cost** |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |
| Total Staff Costs | | |  |
| **Expenses (please detail type, i.e. travel etc)** | | |  |
| **Discounts applied (please detail)** | | |  |
| **Total Overall Cost** | | |  |

**Other costs**

Please state any other costs that will need to be taken into consideration.

|  |  |
| --- | --- |
| **DESCRIPTION** | **COST** £ |
| **1. Other costs (please detail)** |  |
| **2. Other costs (please detail)** |  |
| **3. Other costs (please detail)** |  |
| **TOTAL** |  |

**Discounts, rebates and reductions**

Please detail below any discounts, rebates and other reductions you are prepared to offer and the basis of those incentives

|  |  |
| --- | --- |
| **DESCRIPTION** | **AMOUNT**  £ |
|  |  |
|  |  |
|  |  |
| **TOTAL** |  |

**Total Overall Cost**

Please detail the total fixed cost for the project

|  |  |
| --- | --- |
| **ITEM** | **TOTAL AMOUNT**  £ |
| **Staff Costs** |  |
| **Other Costs** |  |
| **Discounts/reductions** |  |
| **TOTAL Overall Cost** |  |

The following limits will be applicable to all claims for travel and subsistence under this contract:

1. Travel by rail: standard class should be used at all times
2. Travel by car: 45 pence/mile

Hotel bookings should be made through the Environment Agency’s corporate travel contract. Details of this contract are available from the Corporate Contracting Team.

When making reservations you should state that you are a contractor working on Environment Agency business.

Hotel charges must not exceed a maximum limit per night bed and breakfast (VAT included) of: £160 in London; £100 in all other destinations. Please note that these hotel ceiling rates are subject to change throughout the life of the contract.

Expenditure on dinner during an overnight stay must not exceed a maximum limit of £33, including a drink.

Receipts for all rail travel, hotel and food expenses will be required as proof of expenditure and will be reimbursed at cost. No profit or additional cost shall be applied by the contractor to such personal expenses.

**APPENDIX B - PRIOR RIGHTS SCHEDULE**

Details of Prior Rights held by the Parties (To be updated as Rights are introduced during the period of the Contract)

Prior Rights owned or lawfully used by a Party, whether under licence or otherwise, which it introduces to the Project for the purposes of fulfilling its obligations under the Contract.

Held by the Environment Agency

|  |  |  |
| --- | --- | --- |
| **Name and description of Prior Rights** | **Extent of proposed use in the Project** | **Proprietary owner of the Prior Rights** |
|  |  |  |
|  |  |  |
|  |  |  |

Held by the Contractor

|  |  |  |
| --- | --- | --- |
| **Name and description of Prior Rights** | **Extent of proposed use in the Project** | **Proprietary owner of the Prior Rights** |
|  |  |  |
|  |  |  |
|  |  |  |

**Explanation of Contractor's Prior Rights**  
All Intellectual Property Rights owned by or lawfully used by the Contractor, whether under licence or otherwise before the date of this Contract. It can also mean any invention and know how or other intellectual property (whether or not patentable) owned by one of the parties prior to the commencement of the Project, or devised or discovered by one of them only in the course of other projects during the Project period and not arising directly from the Project.

**APPENDIX C – ACCEPTANCE OF TERMS AND CONDITIONS**

I/We accept in full the terms and conditions named in Section 2 and appended to this Request for Quote document.

Company \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Name

Signature \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Print Name \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Position \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Date \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**APPENDIX D – EXAMPLE QSR DOSSIER (additional dossiers can be made available on request.)**

## Piperazine (CAS Number 110-85-0)

Piperazine (PZ) is a cyclic compound with two secondary amine groups. It is solid at room temperature, the anhydrous compound forming white or translucent, rhomboid, or flake like crystals that are highly hygroscopic (ECB 2005). It is water soluble, although its salts differ in their water solubility from very slightly soluble to freely soluble (ECB 2005). It is assumed to be rapidly photolysed in the atmosphere with a calculated half-life of 0.80 hours (ECB 2005) to 2.80 hours (ECHA 2023). In natural waters, it is considered photolytically and hydrolytically stable under environmentally relevant conditions (ECB 2005), although it is inherently biodegradable in water (ECHA 2023).

PZ has been used as a hardener, as a scrubber (gas washing liquid), as a corrosion inhibitor, as an intermediate and a process regulator in the production of industrial chemicals, and in the manufacture of food contact materials. PZ and its derivatives have also been used in insecticides, as an intermediate in the production of human and veterinary medicines as well as previously as an active ingredient in oral anthelmintic drugs (AICIS 2020, ECB 2005)[[1]](#footnote-2), and as a flavouring substance / food additive (Galleria chemica cited in ECB 2005, WHO 2009). Currently, its main source in ambient air is from its industrial applications (ECB 2005, ECHA 2023). New uses for PZ include as a solvent in post-combustion carbon capture systems (Rochelle et al. 2011), where it may be released in small quantities via stack emissions.

Under certain conditions in the atmosphere, secondary amines (e.g., PZ) have the potential to form nitramines (Lag et al. 2009) and nitrosamines (SEPA 2015). Nitrosamine formation is expected with all primary, secondary, and tertiary amines used for carbon capture (Lathouri et al. 2022), with secondary amines having a higher potential to form stable nitrosamines than primary and tertiary amines (Afzal et al. 2017 cited in Lathouri et al. 2022). Formation of breakdown products from stack emissions in air, including nitramines and nitrosamines, should be considered and a separate risk assessment conducted. Nitrosamines can also be potentially formed in the body from the nitrosation of specific amines via an acid- or bacterial catalysed reaction with nitrite, or by reaction with products of nitrogen oxide generated during inflammation and infection (Lag et al. 2009). Evidence is evaluated in this dossier, where inhalation exposure to PZ has been associated with increases in biomarkers for nitrosation observed in urine in occupational and experimental studies.

PZ is registered under EU REACH in the tonnage band ≥ 1 000 to < 10 000 tonnes.

### Regulatory Guidelines

|  |  |
| --- | --- |
| None |  |

### Recommended Environmental Assessment Level in Air

|  |  |
| --- | --- |
| Long-term EAL | 0.015 mg/m3 (15 µg/m3) as daily mean |
| Short-term EAL | None (practical compliance) |

### Overview

PZ (liquid and solid) has a harmonised classification under Annex VI of Regulation (EC) No 1272/2008 (Classification, Labelling and Packaging (CLP) Regulation) for skin corrosion (category 1B; H314), skin sensitization (category 1; H317), respiratory sensitisation (category 1; H334) and reproductive toxicity by oral exposure (category 2; H361fd).

Adverse effects from exposure to PZ have been reviewed by several authoritative bodies (AICIS 2020, ECB 2005, ECHA 2013, and OECD 2004). Studies on the adverse effects following inhalation exposure are very limited.

PZ has shown a low acute toxicity by the oral, dermal, and subcutaneous routes of exposure in *in vivo* studies, but no adequate *in vivo* acute inhalation toxicity data has been found (ECB 2005, OECD 2004). It is a respiratory sensitiser, based on observations in humans, a skin sensitiser based on *in vivo* animal studies, and a corrosive agent (AICIS 2020).

Limited repeat dose inhalation studies in humans or animals have been located. Repeated exposure to PZ by inhalation in human studies may induce chronic bronchitis (Rutter and Voelker 1975 cited in ECB 2005; unnamed study 1975 cited in ECHA 2023).

PZ salts were used extensively in oral anthelmintic drugs from the 1950s in adults and children for treatment durations up to a week (ECB 2005). Reversible neurotoxic effects were observed including abnormal EEG changes, which resulted in a decline in its therapeutic use. While neurotoxicity has also been observed in cats and dogs, ECB (2005) noted that the neurotoxicity observed in human case studies has not been generally reported in rodents.

In oral reproduction and developmental studies *in vivo*, PZ has demonstrated adverse effects on fertility (ECB 2005, OECD 2013), but no symptoms of developmental toxicity (ECB 2005, ECHA 2023).

#### Toxicokinetics

Toxicokinetic data on PZ are limited, although more data on its salts and nitrosated compounds are available (ECB 2005). In occupational settings, inhalation exposure is most likely to the PZ base as either a vapour or solid aerosol. Acknowledging that there were likely to be differences in the bioavailability of the different PZ salts, ECB (2005) noted that there were no indications in the evidence collated that these resulted in significant variations in their toxicological properties. While it was noted that PZ is a strong base (Khalili et al. 2009) and likely to mostly dissociate in acid environments such as the stomach, there was little or no information available on whether it dissociates in the lung, which under normal conditions is slightly alkaline. In pigs (unnamed study 1997 cited in ECHA 2023; Morrison 1997 cited in ECB 2005), radiolabelled (14C) PZ dichloride was readily absorbed from the gastrointestinal tract following administration of 300 mg/kg bodyweight/day by gavage. Peak plasma concentrations were attained one hour after administration, followed by rapid elimination (Unnamed study 1997 cited in ECHA 2023). ECB (2005) concluded that oral absorption was 100%. In the absence of data on respiratory uptake, they also assumed 100% uptake from inhalation exposure.

With respect to distribution, in pigs administered 300 mg/kg bodyweight/day radiolabelled (14C) PZ dichloride by gavage, the highest activity was reported in the kidney and liver (unnamed study 1997 cited in ECHA 2023). Twelve hours post-dosing, elimination of the radiolabelled activity in the kidney was rapid, with only 3% remaining. Elimination from the liver, skeleton, muscle, fat, and skin was slower with 10, 11, 24, and 25%, respectively, remaining after 7 days in comparison with levels at 12 hours post-dosing. ECB (2005) concluded that around 25% of a single administered dose was retained in tissues at seven days after exposure, noting that some metabolites were unidentified.

Metabolism of radiolabelled (14C) PZ dihydrochloride was characterised in pigs following administration of 300 mg/kg bodyweight/day by gavage. Analysis of urine, faeces and tissues showed the presence of mostly unchanged PZ (Morrison 1997 cited in ECB 2005), which is consistent with the findings in humans. ECB (2005) concluded that the principal route of excretion of PZ and its metabolites in animal studies was via urine with only a minor fraction recovered from faeces (16%). Based on the study results presented in the EU REACH dossier, the registrant concluded there was low bioaccumulation potential (ECHA 2023).

The only metabolite consistently identified in urine samples from oral and inhalation animal and human studies using PZ was the nitrosamine N-nitrosopiperazine (NPZ) (ECB 2005). NPZ was detected in gastric juices taken from human volunteers given a single oral dose of 480 mg PZ (Bellander et al. 1985 cited by ECB 2005). In a later paper, Bellander et al. (1988b) estimated the conversion efficiency from PZ to NPZ from this oral dose to be around 0.01%. This is much lower than has been subsequently estimated from repeat dose inhalation studies.

Bellander et al. (1988a) detected NPZ in the urine of eleven workers exposed to anhydrous PZ or PZ hexahydrate vapours at occupational air concentrations ranging from 0.06 to 1.7 mg/m3 for up to a twelve-hour period. In five of the eleven cases, the total amount excreted was 0.3 – 4.7 µg NPZ per person per 24-hour period. In four other cases, the urine levels amounted to <0.2 µg NPZ per 24-hour period, while in the remaining two cases NPZ was not detected in the urine samples. The excretion of PZ in urine was between 100 to 4,700 µg per person per 24-hour period and was strongly correlated to the concentration of PZ in air. Excreted urine concentrations of NPZ were strongly correlated to PZ levels in urine. Urinary NPZ concentrations were not found to be significantly correlated with measured concentrations of nitrite or nitrate in saliva. Workers who smoked did not have higher levels of NPZ in their urine compared to non-smokers. Adjusting for excretion in urine of a maximum of 38% of the absorbed dose as unchanged PZ (as reported by Bellander et al. 1985 cited by ECB 2005), ECB (2005) estimated that the amount of PZ absorbed was between 184 (70/0.38) and 12,400 (4,700/0.38) µg per person per 24-hour period.[[2]](#footnote-3) ECB (2005) concluded that this could indicate a higher rate of conversion from PZ to NPZ for chronic exposures to lower doses, but where the efficiency of NPZ formation decreased with increasing uptake. Using their own “conservative” estimate of 1% conversion for the highest exposure to PZ, ECB calculated a maximum generation of 124 μg NPZ per person over 24-hours (12,400 \* 0.01) (ECB 2005).[[3]](#footnote-4) Citing earlier work that stated that around 10% of NPZ was excreted unchanged in urine (Tricker et al. 1991 cited by ECB 2005), ECB (2005) concluded that the maximum predicted NPZ urine levels of 12.4 µg per person per 24-hour period (124 \* 0.1) were in reasonable agreement with the highest NPZ urine levels of 4.7 µg per person per 24-hour period observed in Bellander et al. (1988a).

In a subsequent experimental study, Bellander et al. (1988b) investigated the urinary levels of NPZ in four volunteers exposed to between 0.25 – 0.30 mg PZ/m3 under experimental conditions with diets containing nitrate- and ascorbate-rich foodstuffs such as spinach, beetroot, and citrus fruits such as lemon juice. Exposure to PZ vapour took place in an air chamber in two four-hour periods with an hour between them. Air was sampled each hour. Urine samples were taken every 4 hours, and 4, 16, 24, and 40 hours after the end of exposure. The approximate nitrate content of the three diets ranged from 30 - 900 mg/day and the ascorbate content ranged from 30 – 330 mg/day. Unlike the earlier occupational study (Bellander et al. 1988a), PZ urinary levels were not correlated with air concentration, but the variations in air concentrations were small. Most excretion occurred during and up to 24-hours after exposure. NPZ was found in urine and the levels impacted by the dietary intake of nitrate and ascorbate. Bellander et al. (1988b) speculated that an observed mean excretion level of 0.4 mg PZ per person was consistent with around 36% of the total exposure dose (around 1.1 mg) being excreted unchanged (assuming 100% absorption). The highest observed excretion of NPZ in this study was 1.7 µg per person after 32-hours. Referring to an earlier (unreferenced) study, Bellander et al. (1988b) inferred that the total amount of NPZ formed in the body over this period was about 50 µg per person. They concluded that this was equivalent to a conversion rate from PZ to NPZ of around 5% [ (50 µg NPZ / 1100 µg PZ) \* 100].[[4]](#footnote-5)

Several human studies have examined excretion of PZ and its salts following oral administration, although the non-specific chemical colorimetric method used by older studies may be unreliable (ECB 2005). When 480 mg of PZ was administered to four volunteers over a period of 16 hours, 19 – 35% of the administered dose was recovered unchanged in urine, with a further 2-3% excreted over an additional 24-hour period (Bellander et al. 1985 cited by ECB 2005). No information on excretion of PZ in human faeces was reported (ECB 2005).

#### Short- and Long-term Exposures

Short- and long-term inhalation and oral studies in animals and humans are limited.

Only limited data has been reported on the acute toxicity of PZ via inhalation (AICIS 2020, ECB 2005). In a study similar to OECD TG 403 (no further details provided), rats were exposed (whole body) to a single dose of PZ vapours at 1.61 mg/L (1,610 mg/m3) for eight hours (AICIS 2020). There were no mortalities, the animals reportedly exhibiting only a slight mucosal irritation. AICIS (2020) concluded that the LC50 was therefore >1,610 mg/m3 (the highest reported dose).

In acute oral toxicity studies conducted according to OECD TG 401 or equivalent, PZ had a low toxicity, with reported LD50 values in rats of 2,300-2,600 mg/kg bodyweight (Unnamed studies 1964, 1980, 1981 cited in ECHA 2023). Available human data reported a ‘probable oral lethal dose’ of 5–15 g/kg bodyweight (HSDB cited in AICIS 2020).

PZ is a skin sensitiser causing allergic dermatitis and a respiratory sensitiser (ECB 2005). No animal data were available to support the classification as a respiratory sensitiser, which was based on case reports in humans (AICIS 2020).

PZ salts were used extensively in anthelmintic drugs from the 1950s at recommended doses of around 100 mg/kg body weight for adults and up to 65 mg/kg body weight for children for treatment durations up to a week (ECB 2005). Reversible neurotoxic effects including muscular weakness, unsteadiness, lack of co-ordination, hypotonia, diminished tendon reflexes, but also tremors, clonic spasms, dysarthria, diffuse EEG disturbances, mental confusion and hallucinations were observed. This has led to a decline in its therapeutic use.

ECB (2005) summarised a number of clinical case studies that taken together “*offered convincing evidence for PZ neurotoxicity at recommended doses without predisposing factors present*… *The fact that only a minority of all patients in the [larger] studies developed neurotoxicity, cannot be cited as evidence against a causal association, but rather reflects large differences in individual sensitivity, a well-known observation that must be taken into consideration.*” In a clinical case study, Belloni and Rizzoni (1967 cited by ECB 2005) investigated 11 children treated with PZ hexahydrate at a dose of 35 mg/kg body weight/day PZ base for five days. Abnormal EEG changes were noted that were similar to those previously described in the literature (continuous bilateral spikes and polyspikes and high-voltage waves interspaced with slow-wave activity). In a study by Padelt et al. (1966 cited by ECB 2005), a cohort of 89 children (most children were aged 1-3 years) including 41 boys and 48 girls, who had been hospitalised mostly for infectious diseases and later treated for pinworm infection, were treated with PZ hexahydrate about ten days after the main acute illness had subsided. The children were given a single dose equivalent to a total daily dose of 110 mg/kg body weight/day (ECB 2005). No visible signs of neurotoxicity were observed. In 56 children (63%) the EEG changes could be classified into Category A (no or light effects), and in 33 (37%) in Category B (moderate to severe changes). No association between abnormal EEG pattern and infectious disease or age was noted.

Neurotoxic side effects in animals treated with anthelmintic formulations of PZ (recommended dose in cats and dogs is 45–65 mg/kg body weight) have also been reported (ECB 2005, AICIS 2020). Neurological effects in dogs included acute distress, ataxia, head, and neck stretched out, front legs pulled back along the chest wall, and hind legs stretched outwards. Felidae species (cats, tigers, lions) appeared to be more sensitive to piperazine and have showed effects including lethargy, clonic seizures, and lack of muscular coordination with ataxia (ECB 2005, AICIS 2020).

ECB (2005) noted that the neurotoxicity observed in human case studies has not been generally observed in short- or long-term animal studies in rodents (see below).

Limited repeat dose inhalation studies in humans or animals have been located. Repeated exposure to PZ by inhalation in human studies may induce chronic bronchitis, but no Low Observed Adverse Effect Concentration (LOAEC) or No Observed Adverse Effect Concentration (NOAEC) was established (Rutter and Voelker 1975 cited in ECB 2005; unnamed study 1975 cited in ECHA 2023).

In a dietary study, PZ dihydrochloride was administered to beagle dogs at doses up to 3,692 ppm (approximately 122 mg/kg body weight/day) for 13 weeks, no clear Low Observed Effect Level (LOEL) could be established (Rutter and Voelker 1975 cited by ECB 2005). Except for signs of possible mild hepatic involvement, examination of clinical parameters, behaviour, body weight changes, organ weights, gross and microscopic pathology as well as ophthalmoscopic findings gave no indication of compound-related systemic toxicity. All dogs showed slight to moderate body weight gains and food consumption was generally comparable between test and control animals. For liver toxicity, a No Observed Adverse Effect Level (NOAEL) of 25 mg/kg body weight/day PZ base was proposed. ECB (2005) noted “surprise” that symptoms of neurotoxicity had not been observed in the animals since the dosing regime in this study was consistent with levels found to cause symptoms in animals treated with anthelmintic drugs.

In a 90-day dietary study, groups of male and female rats were given either anhydrous PZ at doses corresponding to 50, 150, and 500 mg/kg body weight/day PZ base or PZ dihydrochloride at doses of 45, 140, and 450 mg/kg body weight/day PZ base (Lockwood 1957 cited by ECB 2005). For anhydrous PZ, degenerative changes of the liver with diffuse cloudy swelling and focal necrosis as well as fibrotic and degenerative changes in the kidneys were reported at 500 mg/kg body weight/day and “somewhat milder” changes at 150 mg/kg body weight/day. A NOAEL of 50 mg/kg body weight/day was reported. No adverse effects were observed for PZ dihydrochloride, which ECB (2005) suggested casted significant doubts over the study findings.

In a 90-day feeding study (following US FDA standards and GLP compliant), Sprague Dawley rats were administered PZ dihydrochloride at 0, 400, 1200 or 2,394 mg/kg body weight/day. Apart from a dose related decrease in body weight gain, no adverse effects were observed during the study (AICIS 2020). A NOAEL of 1,200 mg/kg bodyweight/day (equivalent to 627 mg/kg body weight/day as PZ) was determined.

Systemic toxicity has also been observed in several more recent reproductive and developmental toxicity studies (see below for more experimental details). A NOAEL of 420 mg/kg/day was reported for pregnant rats based on excessive salivation, lethargy and a reduction in body weight gain, body weight, as well as food consumption in animals fed by gavage during Gestation Days (GD) 6-15 (Ridgway 1987b cited by ECB 2005). A NOAEL of 42 mg/kg body weight/day was reported for pregnant rabbits based on decreased food consumption and body weight gain during the first four days of dosing by gavage (Ridgway 1987b cited by ECB 2005). In a reproductive and developmental toxicity study (conforming to OECD TG 416), Sprague Dawley CD rats were administered PZ dihydrochloride in the diet throughout maturation, mating, gestation, and lactation phases for two successive generations (Wood and Brooks 1994 cited by ECB 2005 and AICIS 2020). There was clear evidence of toxicity at the highest dose in both generations indicated by reduced body weight gain, reduced number of pregnancies (significant only in F1) and reduced litter size. Developmental effects were also noted including delayed sexual maturation in F1 animals (age at vaginal opening in females and preputial separation in males), but AICIS (2020) considered that this could be related to a decreased body weight. Reduced body weights and food consumption were noted at 300 mg/kg body weight/day, along with reduced litter size in both generations, reduced implantation sites in F1 and delayed sexual maturation in F1. No treatment-related effects were reported at 125 mg/kg body weight/day. A NOAEL of 125 mg/kg body weight/day and a Low Observed Adverse Effect Level (LOAEL) of 300 mg/kg body weight/day were established for maternal toxicity (ECB 2005, AICIS 2020). In a developmental toxicity study (non-guideline), Charles River CD(SD)BR female rats were treated by gavage with PZ phosphate at doses of 105, 420 and 2,100 mg/kg body weight/day PZ base during Gestation Days (GD) 6 – 15 (Ridgway 1987b cited by ECB 2005). Signs of maternal toxicity included excessive salivation, lethargy, reduced food consumption and body weight gain at the highest dose. No teratogenic effect was reported, but foetal weights were reduced (ECB 2005, AICIS 2020). In another developmental toxicity study (GLP compliant), groups of 16 New Zealand White female rabbits were orally administered PZ phosphate suspended in 1% w/v methyl cellulose at 0, 42, 94 and 210 mg/kg body weight/day PZ base from GD 6–18 of gestation (Ridgway 1987a cited by ECB 2005). Signs of maternal toxicity at the highest dose included neurotoxicity (excessive salivation and nervousness), anorexia, reduced food intake (by 85 % during days 6–14), reduced faeces production and body weight, abortion (in one female) and intestinal abnormalities (in two females killed in extremis). A LOAEL of 94 mg/kg body weight/day for maternal toxicity was determined based on transiently reduced body weight gain, food consumption (-39 %) and faeces production. A NOAEL of 42 mg/body weight/day was reported (ECB 2005). Teratogenic effects included a high rate of post-implantation loss (100% resorption in four litters), reduced foetal weight, slight retardation in ossification, major abnormalities in 23% of foetuses (cleft palate, umbilical hernia) and increased incidence of poorly ossified hindlimbs, all at the highest dose. The study suggested that teratogenic effects could be secondary to maternal toxicity, due to reduced food intake (ECB 2005, AICIS 2020). As a result, ECB (2005) recommended a harmonised classification for PZ under CLP for reproductive and developmental toxicity (category 2; H361fd).

#### Pivotal Studies

The pivotal study used in the derivation of the short-term Derived No-Effect Level (DNEL) for systemic and local effects in workers following inhalation (ECHA 2023) was not specified. The DNEL was derived from an unreferenced Occupational Exposure Level (OEL), based on respiratory tract sensitisation.

The point of departure (POD) of 30 mg/kg bodyweight/day used for risk characterisation by ECB (2005) was taken from a clinical study by Belloni and Rizzoni (1967 cited by ECB 2005). After treatment of a four-year-old child for 3 days with 100 mg/kg body weight PZ hexahydrate (44 mg/kg body weight PZ base), severe asthenia, tottering gait, poor balance, extreme muscular weakness, and EEG changes developed. This first case caused the clinic to investigate all children under treatment with PZ. In ten out of eleven children treated with PZ hexahydrate at 35 mg/kg body weight/day PZ base for five days, abnormal EEG changes were noted that were similar to those previously described in the literature (including continuous bilateral spikes and polyspikes and high-voltage waves interspaced with slow-wave activity). Only one of the children was reported to suffer from clinical abnormality that could cause confounding (enlarged liver due to chronic cardiac failure). Upon repeated treatment, after normalisation of the EEG, 6 of the children were treated with PZ hexahydrate at the same dose together with 1 mg/kg body weight/day prednisone and EEG changes either did not appear or were reported to be less pronounced. ECB (2005) regarded the POD of 30 mg/kg body weight/day as not a “true LOAEL” since it was based on the therapeutic dose and there was little information reported on effects lower than this dose. The human toxicity data was considered more relevant than a POD from repeat dose animal studies because of its greater relevance to human health and greater seriousness compared to milder hepatic effects (ECB 2005).

The pivotal study used by EMEA (2001) to set an acceptable daily intake (ADI) for veterinary medicinal products was a sub-chronic study in Beagle dogs (Rutter and Voelker 1975 cited by ECB 2005). In a dietary study, PZ dihydrochloride was administered in the feed to groups of 8 dogs (4 females and 4 males) at levels of approximately 1.5, 6, and 25 mg/kg body weight/day PZ base. For the high dose group, PZ dihydrochloride was administered at about 25 mg/kg body weight/day PZ base from week 1 through 5 and about 63 mg/kg body weight/day PZ base from week 6 through 13. A fourth group served as a control. Appearance and behaviour, body weight changes, clinical laboratory data, ophthalmoscopic findings, organ weights, as well as gross and microscopic pathology were recorded. All animals were observed daily for appearance, behaviour, appetite, elimination, and signs of toxic or pharmacological effects. Individual body weights, food and test compound consumption were recorded weekly for the duration of the study. Clinical laboratory studies were performed on all dogs initially, and at 4 and 13 weeks. Gross pathology was performed on all dogs following sacrifice, and the following organ weights were measured for each sacrificed dog and the organ/body weight ratios subsequently determined: thyroid, liver, spleen, kidney, adrenal and testis with epididymis. Histopathological examination included brain, thoracic spinal cord, pituitary, thyroid, adrenal, heart, lung, spleen, liver, kidney, stomach, small and large intestines, pancreas, ovary, uterus, prostate, salivary gland, mesenteric lymph nodes, urinary bladder, gallbladder, nerve with muscle, eye, bone marrow, and rib junction. Except for signs of possible mild hepatic involvement, examination of clinical parameters, behaviour, body weight changes, organ weights, gross and microscopic pathology as well as ophthalmoscopic findings gave no indication of compound-related systemic toxicity. All dogs showed slight to moderate body weight gains and food consumption was generally comparable between test and control animals. After 4 weeks, serum glutamic-oxaloacetic transaminase (SGOT) values were significantly higher in the exposed males in comparison with controls, but the SGOT values had returned to normal after 13 weeks. At 13 weeks, there was indication of an elevation of this biomarker in the intermediate and high dose females. There were no significant effects on alkaline phosphatase, or on the serum glutamic pyruvic transaminase (SGPT) values in any of the exposed groups. Interpretation of the SGOT data was hampered by the low number of animals in each group, as well as by the significant drift in base-line values found in the control group at the start of the study, after 4, and 13 weeks respectively. In males, but not in females, there was a dose related trend for increase in absolute liver and spleen weights, but no significant differences in comparison with controls for organ weight/body weight ratios could be noted. All other organ weights and organ/body weight ratios were within historical laboratory limits and comparable to control values. Gross and microscopic pathology did not reveal any organ or tissue alterations that could be attributed to the administration of the test material. Although the report states that “All animals were observed daily for appearance, behaviour, appetite, elimination, and signs of toxic or pharmacological effects”, the study failed to identify neurotoxic effects of PZ in the dog, although the highest dosage (145 mg/kg body weight/day for 8 weeks) was considered by ECB (2005) to exceed the dose, as well as the time of administration that have been described in the veterinary literature to induce serious signs of neurotoxicity in dogs such as ataxia, muscular weakness, head pressing, hyperesthesia, and an unusual myoclonus (head and neck stretched out, front legs pulled back along the chest wall, and hind legs stretched outwards and back). Based on this study, the EU Committee for Veterinary Medicinal Products identified a NOAEL of 25 mg/kg body weight/day PZ base for mild liver effects.

#### Genotoxicity and Carcinogenicity

#### Genotoxicity data

##### In vitro data

Several *in vitro* assays have been carried out in bacterial and mammalian cells to assess the genotoxic potential of PZ (AICIS 2020, ECB 2005, ECHA 2023, OECD 2004).

Negative results were reported in four bacterial reverse mutation assays (similar to OECD TG 471) using *Salmonella typhimurium* strains TA 1535, TA 1537, TA 97, TA 98, and TA 100 with and without metabolic activation, up to the highest dose tested of 10,000 µg/plate (Unnamed studies 1980, 1983, 1986 and Haworth et al. 1983 cited in ECHA 2023).

Negative results were reported in an *in vitro* mammalian chromosome aberration test (similar to OECD TG 473) using Chinese hamster ovary (CHO) cells with and without metabolic activation, up to the highest dose tested of 110 µg/ml (Unnamed study 1986 cited in ECHA 2023).

Negative results were reported in an *in vitro* mammalian cell gene mutation test (similar to OECD TG 476) using mouse lymphoma L5178Y cells with and without metabolic activation, up to the highest dose tested of 400 µg/ml (Unnamed study 1987 cited in ECHA 2023). Positive results were reported in an *in vitro* mammalian cell gene mutation test (no guideline followed) using mouse lymphoma L5178Y cells with metabolic activation at the highest dose tested of 500 µg/ml where there was clear cytotoxicity (unnamed study 1980 cited in ECHA 2023). Negative results were reported at 400 µg/ml.

Negative results were reported in a mammalian cell transformation assay (following EU Method B.21) using BALB/3T3 mouse cells at doses up to 300 μg/ml (no data on metabolic activation) (Unnamed study cited 1980 in ECHA 2023).

##### In vivo data

No *in vivo* genotoxicity studies are available on PZ, but a small number of studies have been conducted using its salts (AICIS 2020).

Negative results were reported in an *in vivo* micronucleus test, carried out according to OECD TG 474, in male and female CD-1 mice (5/sex/group) that received a single oral dose (5000 mg/kg bodyweight) of PZ dihydrogen phosphate[[5]](#footnote-6)) (Unnamed study 1987 cited in AICIS 2020).

Negative results were reported in a host-mediated *Salmonella typhimurium* (TA 1950) mouse assay (similar to OECD TG 474) in which NMRI mice were administered 1450–2900 μmol/kg body weight of PZ dihydrochloride by gavage. However, when the salt was co-administered with nitrite, it induced a positive response (no further details available) at all doses (Braun et al. 1977 cited in AICIS 2020, ECB 2005).

A cohort study in male Swedish workers exposed mainly to PZ indicated a modest but significant increase in the incidence of micronuclei in cultured peripheral lymphocytes compared with control subjects (Hogstedt et al. 1988 cited in AICIS 2020, ECB 2005). The interpretation and significance of the results from the study were stated as uncertain because numerous other organic chemicals were manufactured in the same plant, including genotoxic agents such as ethylene oxide, from which PZ was synthesised. ECB (2005) stated that no further detail on the other organic chemicals, which could result in significant confounding effects on the results reported, were provided in the reported study.

Other studies in workers exposed to mixtures of chemicals including PZ showed no difference in the incidence of micronuclei and chromosome aberrations in lymphocytes between exposed workers and unexposed control subjects (Hagmar et al. 1988; Pero et al. 1988 cited in AICIS 2020).

##### Overall genotoxicity conclusion

The available data from epidemiological, *in vivo*, and *in vitro* studies indicate PZ alone is not genotoxic. Some evidence is available to indicate that PZ in the presence of nitrosating agents may be genotoxic.

#### Carcinogenicity data

No reliable human epidemiology studies were found in the reviewed literature. Available animal carcinogenicity studies with PZ did not meet current standards in most respects (ECB 2005), but they are nonetheless summarised below.

Groups of MRC rats (n=15/sex) were administered 0.025% of PZ in drinking water (equivalent to 20 – 25 mg/kg body weight/day) for 5 days per week for 75 weeks. No increase in incidence of any tumours relative to controls was reported by the authors (Lijinsky 1973 cited by ECB 2005).

In a dietary study, Swiss mice (40/sex/group) were administered 6.25 g/kg in feed (equivalent to 938 mg/kg body weight/day) PZ, alone or together with 1,000 mg/L sodium nitrite in drinking water for 5 days per week for 28 weeks (Greenblatt et al. 1971 cited by ECB 2005). They were subsequently observed for a further 12 weeks. PZ alone produced no effect, but administration with sodium nitrite induced a significant increase in the percentage of adenoma-bearing mice (64%) and lung adenomas per mouse ((1.8 ± 2.2) compared with controls (80/sex). There was no increase in any other type of tumour and the data for the sexes was not reported separately. The authors concluded that *in vivo* nitrosation of PZ to NPZ in the stomach was responsible for the carcinogenicity observed. ECB (2005) noted that “…*spontaneous incidences of lung adenomas up to 50% in females have been reported for certain strains of Swiss mouse*.”

In a subsequent study in strain A mice (Greenblatt and Mirvish 1973 cited by ECB 2005), varying doses of PZ were administered with the feed (equivalent to 104 to 2,820 mg/kg body weight/day) together with a constant concentration of nitrite in drinking water (1,000 mg/L) to groups of 40 animals per sex for 5 days per week for 25 weeks with sacrifice after another 13 weeks post exposure. In a second series of experiments in the same study, various amounts of nitrite were given in drinking water (50 -2,000 mg/L), keeping the PZ concentration in food at a constant level of 938 mg/kg feed. At nitrite levels >50 mg/L, an elevation in lung adenomas was seen for all combined exposures. ECB (2005) noted again that “*no data for other types of tumours were reported*” and that “*…the strain A mouse has long been known to be extraordinarily susceptible to induction of adenomas of the lung by a host of initiating as well as cancer promoting substances.*” They further concluded that “… *the background incidence in controls was high also in this case, as well as it was strikingly variable (32% of control mice with adenomas in the first experiment, and 13% in the second), possibly indicating lack of randomisation of the animals with respect to the dosage groups. For the above-mentioned reasons, it is very difficult to draw any valid conclusions from these studies*.”

##### Conclusion

IARC have not evaluated the carcinogenicity of PZ.

Although the data is limited, ECB (2005) cautiously concluded PZ is not considered to be carcinogenic itself in the absence of nitrosating agents. This was primarily based on a lack of genotoxic action.

Secondary amines can form N-nitrosamines and N-nitramines under certain conditions. Nitrosamines have well documented mutagenic and carcinogenic effects, whereas there are limited data for nitramines, although they have been found to be carcinogenic by deamination to formaldehyde and ammonia both *in vivo* and *in vitro* (Ravnum et al. 2014). N-nitramines are structurally related to nitrosamines, and due to this similarity, there has been a general interest in the potential mutagenicity and carcinogenicity of the N-nitramines (Lag et al. 2011).

The only metabolite consistently identified in urine samples from oral and inhalation animal and human studies was the nitrosamine NPZ (ECB 2005).

Nitrosation has been noted in dietary rodent studies, where PZ and a nitrosating agent (usually a nitrate or nitrite salt) have been co-administered. However, ECB (2005) noted the following reservations for the interpretation of nitrosation experiments in rodents. Whereas the pH of the rodent stomach was considered to be close to the optimum pH for nitrosation of amines (Mirvish 1982 cited by ECB 2005), the human stomach had a less favourable and higher acidity. The nitrite co-doses used in the dietary studies were also considered unrealistic (ECB 2005).

More importantly, there is evidence that inhalation exposure to PZ and its salts (see earlier Toxicokinetics section) also results in the formation of NPZ in humans (both in occupational and volunteer studies). ECB (2005) concluded that a higher rate of conversion from inhaled PZ to NPZ may result from chronic exposures to lower doses. ECB (2005) assumed a “worst-case” conversion rate of 1%, but the findings of work by Bellander et al. (1988b) suggested that this could be as high as 5%. It is important to note the approximate nitrate content of the three diets used by Bellander et al. ranged from 30 – 900 mg/day. EFSA (2017b) estimated that the mean exposure to nitrate from all dietary sources for a 70 kg adult ranged from 75 to 165 mg/day and the high-level consumption (95th percentile) ranged from 165 to 370 mg/day. Therefore, the low nitrate diets considered by Bellander et al. (1988b) are relevant to typical population exposures.

Bercu et al. (2023) reviewed the potential carcinogenic risk from ingestion of small molecule nitrosamines in pharmaceuticals including NPZ. They concluded that it is mutagenic *in vitro* and a multi-organ carcinogen in rodent studies. They derived a TD50 of 28.5 mg/kg bodyweight/day from a study by Love et al. (1977 cited by Bercu et al. 2023), where rats were administered with approximately 18.8 and 37.6 mg/kg bodyweight/day in drinking water for 5 days per week over their lifetime. This study identified the nasal cavity and to a lesser extent the liver as the most sensitive target organs for tumours. Consistent with other nitrosamines, the mode of action for its carcinogenicity was considered to be via the diazonium ion (Bercu et al. 2023). The data from the Love et al. (1977) has been reviewed and a BMDL10 of 2.7 mg/kg bw/day[[6]](#footnote-7) for nasal tumours derived.

Although ECB (2005) concluded that PZ itself was not a carcinogen, there is clear evidence that the carcinogenic nitrosamine NPZ forms *in vivo* following inhalation of PZ (Bellander et al. 1988a and 1988b). Bellander et al. (1988b) suggested that the site of NPZ formation is the stomach, noting that due to its “… *high water solubility, PZ is readily absorbed in the airways, from where it can reach the stomach either by Mucociliary clearance followed by swallowing or by pulmonary absorption followed by intragastric secretion*”. The formation of NPZ from the combination of inhalation of PZ and dietary exposure to nitrites and nitrates (the nitrosation agent) has been considered in the derivation of the long-term EAL.

### Authoritative opinion for short-term exposure

The EU REACH registrants (ECHA 2023) proposed an inhalation health-based guidance value (HBGV) for workers only.

#### EU REACH Chemical dossier

##### Workers: short-term inhalation exposure – local and systemic effects

The EU REACH dossier for PZ (ECHA 2023) on the ECHA dissemination portal[[7]](#footnote-8) derived a DNEL of 300 µg/m3 (0.30 mg/m3) for short- term inhalation exposure to protect workers, based on local and systemic effects.

The EU REACH dossier stated that deriving NOAELs from available data would result in a DNEL that would be higher than the OEL (reference not stated[[8]](#footnote-9)). Therefore, the short-term (15-minute reference period) workplace exposure limit was used as the DNEL. This is based on respiratory tract sensitisation, although the pivotal study used to derive the OEL is not detailed in ECHA (2023) or HSE (2020).

### Authoritative opinion for long-term exposure

No inhalation based HBGV for the protection of the general public were identified. EMEA (2001) has proposed an oral HBGV for the use of PZ in veterinary medicinal products and the EU REACH registrants (ECHA 2023) have proposed an oral HBGV for workers.

#### European Agency for the Evaluation of Medical Product

EMEA (2001) proposed an ADI of 0.25 mg/kg body weight/day for veterinary medicinal use.

A NOAEL of 25 mg/kg body weight/day was determined from a repeat dose oral study (Rutter and Voelker 1975 cited in ECB 2005) based on liver toxicity in Beagle dogs following exposure to doses of 0, 1.5, 6 or 25 mg/kg body weight/day piperazine base in the diet for 13 weeks. The NOAEL was divided by a safety factor of 100 (no further details) to give the ADI of 0.25 mg/kg bodyweight/day.

#### EU REACH Chemical dossier

##### Workers: long-term inhalation exposure – local and systemic effects

The EU REACH dossier for PZ accessed through the ECHA dissemination portal (ECHA 2023) derived a DNEL of 100 µg/m3 (0.10 mg/m3) for long-term inhalation exposure to protect workers, based on local and systemic effects.

The EU REACH dossier stated that deriving NOAELs from available data would result in a DNEL that would be higher than the OEL (reference not stated7). Therefore, the long-term exposure limit (8-hour reference period) workplace exposure limit was adopted as the DNEL. This is based on respiratory tract sensitisation, although the pivotal study used to derive the OEL is not detailed in ECHA (2023) or HSE (2020).

### Summary

One authoritative body EMEA (2001) and EU REACH registrants (ECHA 2023) have proposed HBGVs.

Only the EU REACH dossier for PZ proposed a short-term HBGV of 0.30 mg/m3 for inhalation exposure based on the protection of workers from local and systemic effects (ECHA 2023). The DNEL was based on the OEL for short-term exposure (15-minute reference period), the derivation of which is not presented, but it is reportedly based on respiratory tract sensitisation.

A long-term DNEL of 0.1 mg/m3 was derived in the EU REACH dossier (ECHA 2023) for the protection of workers from inhalation exposure. The DNEL was based on the OEL for long-term exposure (8-hour reference period) for respiratory tract sensitisation. No further details were provided. An ADI was also proposed by EMEA (2001) for the oral use of PZ in veterinary medicinal products. EMEA (2001) based the ADI of 0.25 mg/kg body weight/day on a 13-week dietary study in Beagle dogs (Rutter and Voelker 1975 cited in ECB 2005) from which a NOEL of 25 mg/kg body weight/day was determined based on liver toxicity.

### Recommendations

#### Short-term EAL

No authoritative short-term HBGVs for inhalation exposures for the general population have been derived. The DNEL for workers was not considered a suitable basis for the short-term EAL.

A short-term EAL of 0.15 mg/m3 as a 24-hour mean is proposed to protect the public.

ECB (2005) summarised a number of clinical case studies that taken together “*offered convincing evidence for PZ neurotoxicity at recommended* [oral] *doses without predisposing factors present… The fact that only a minority of all patients in the [larger] studies developed neurotoxicity, cannot be cited as evidence against a causal association, but rather reflects large differences in individual sensitivity, a well-known observation that must be taken into consideration.*” The human toxicity data was considered more relevant than POD from repeat dose animal studies because of its greater relevance to human health and greater seriousness compared to milder hepatic effects. The short-term EAL of 0.15 mg/m3 was derived from the clinical case study (Belloni and Rizzoni 1967 cited by ECB 2005), where abnormal EEG changes were observed in children prescribed PZ hexahydrate at a dose of 35 mg/kg body weight/day PZ base for five days. ECB (2005) regarded the approximate 30 mg/kg body weight/day as an effect level as it was based on the therapeutic dose. Assuming 100% bioavailability by both the inhalation and oral routes (as assumed by ECB 2005), this can be converted to a LOAEC of 45 mg/m3 by assuming a young child inhales 10 m3 per day and weighs 15 kg. Considering the commentary by ECB (2005), a total UF of 300 was applied (a factor of 10 for intraspecies variation, a factor of 10 for extrapolation from LOAEC to NOAEC, and a factor of 3 for the quality of the database).

#### Long-term EAL

No authoritative long-term HBGVs for inhalation exposures have been derived. The DNEL for workers was not considered a suitable basis for the long-term EAL.

A long-term EAL of 0.015 mg/m3 as a 24-hour mean is proposed to protect the public.

ECB (2005) identified the importance of neurotoxicity in clinical case studies in humans, which is not observed in rodent laboratory studies. There is a lack of dose-response information. A long-term EAL of 0.015 mg/m3 was derived from the clinical case study (Belloni and Rizzoni 1967 cited by ECB 2005), where abnormal EEG changes were observed in children prescribed PZ hexahydrate at a dose of 35 mg/kg body weight/day PZ base for five days. ECB (2005) regarded the approximate 30 mg/kg body weight/day as an effect level as it was based on the therapeutic dose. Assuming 100% bioavailability by both the inhalation and oral routes (as assumed also by ECB 2005), this can be converted to a LOAEC of 45 mg/m3 by assuming a young child inhales 10 m3 per day and weighs 15 kg. Considering the commentary by ECB (2005), a total UF of 3,000 was applied (a factor of 10 for intraspecies variation, a factor of 10 for extrapolation from LOAEC to NOAEC, a factor of 10 to extrapolate to chronic exposures, and a factor of 3 for the quality of the database).

This value is protective of other toxic effects and potential carcinogenicity resulting from conversion of PZ to NPZ following inhalation.

### Practical Compliance Constraints

Depending on the toxicity of a substance, both a short- and long-term EAL may be appropriate, reflecting adverse effects to health over different exposure periods. Notwithstanding the possible differences in the toxicology (dose-response and endpoints) between potential short-term and long-term health effects, there is a practical limit on the value of a short-term EAL if the long-term EAL or statutory value is not to be exceeded. The limit depends on whether the long-term EAL is based on either a threshold or a non-threshold health effect.

**Thresholded Effects**

The long-term EAL is usually based on a 24-hour time weighted mean concentration. The highest short-term air concentration that will not exceed the long-term EAL can be estimated by multiplying the long-term value by 24 for a short-term hourly upper limit. There is no short-term daily upper limit.

Any proposed short-term EAL should be less than the appropriate daily or hourly upper limit to be useful without any practical constraint imposed by the need to ensure compliance with the long-term EAL or statutory value. If a recommended short-term EAL is equal to or exceeds the upper limit, then it is assumed that compliance with the long-term EAL will be protective of short-term exposures and health effects.

In the case of piperazine (PZ), the proposed short-term EAL of 0.15 mg/m3 (24-hour mean) exceeds the long-term EAL of 0.015 mg/m3 (24-hour mean) based on a threshold effect. Therefore, due to the requirements for practical compliance, no short-term EAL is proposed.

## Selenium and its compounds (CAS Number 7782-49-2)

Selenium is a ubiquitous non-metal element (IPCS 1987), which forms variable oxidation state compounds, the most common of which are selenite (+4), selenate (+6) and selenide (-2). It is used to colour glass or ceramics, in semi-conductor diodes, in photoelectric cells, shampoos, to improve the properties of metal (steel) alloys, as a catalyst in the chemical industry, as an additive to dyes, plastics and lubricants, in the rubber industry and in clinical treatment (de Groot 2009). Significant atmospheric emissions of selenium dioxide result from the combustion of coal and metal smelting, but it is rapidly transformed into elemental selenium by atmospheric reactions (Wen and Carignan 2007). The principal route of human exposure is via the diet, where selenium forms important amino acids including selenomethionine and selenocysteine (EFSA 2014). Hydrogen selenide is a colourless gas with a foul pungent odour (SCOEL 1992), whose main uses were in the electronic and photovoltaic industries. In line with the previous EAL derivation, hydrogen selenide is not included in this review.

### Regulatory Guidelines

|  |  |
| --- | --- |
| None |  |

### Recommended Environmental Assessment Level in Air

|  |  |
| --- | --- |
| Long-term EAL | 0.002 mg/m3 (2 µg/m3) as a 24-hour mean |
| Short-term EAL | Not recommended (insufficient evidence) |

### Overview

Adverse effects from exposure to selenium and its compounds have been reviewed by a few authoritative bodies (ATSDR 2003, EA 2009, EVM 2003, IPCS 1987, US EPA 1991, WHO 2011). Selenium is an essential element in humans and animals, where it is a component of the enzyme glutathione peroxidase, and an antidote to the toxic effects of other trace metals including mercury, cadmium, and arsenic (de Groot 2009). There is limited evidence on its inhalation toxicity, but selenium dust is a strong irritant of the upper respiratory tract and lungs (ATSDR 2003). Evidence for systemic toxicity comes from epidemiological studies of excessive dietary exposure (ATSDR 2003, EA 2009, EVM 2003, US EPA 1991, WHO 2011), which resulted in selenosis, whose symptoms include the dermal and neurological effects of diseased nails, skin, and hair loss, as well as an unsteady gait and paralysis.[[9]](#footnote-10)

#### Toxicokinetics

Animal studies indicate that selenium is extensively absorbed after inhalation exposure with the rate of uptake dependent on chemical form and particle size (ATSDR 2003). When supplied as selenomethionine and selenocysteine, oral absorption is close to 90% (EFSA 2014), but although inorganic forms are well absorbed, the rates are closer to 50% (EA 2009). Selenite has been observed to be better absorbed than selenate, but retention of selenium from these two species appears to be similar (EFSA 2014). Absorption efficiency does not seem to be affected by selenium status or play a role in the homeostatic regulation of selenium (ATSDR 2003, EFSA 2014).

In blood plasma, the most abundant selenoproteins with known functions are SEPP1 and extracellular glutathione peroxidase, typically accounting for approximately 30–60 % and 10–30 % of selenium, respectively (EFSA 2014). The rest of plasma selenium consists of selenomethionine in albumin and other proteins and a minor fraction (< 3 %) in small molecular compounds such as selenosugars. Studies in rodents have demonstrated a hierarchy amongst the selenoproteins, with preferential incorporation of selenium into certain selenoproteins and the prioritisation of selenium supply to specific organs, in particular the brain and the reproductive and endocrine organs (EFSA 2014). The thyroid gland has the highest selenium concentration, followed by the kidneys, testes, and liver. Skeletal muscles account for the majority of body content (30–50 %), while less selenium is contained in the bones (15 %), blood (10 %), liver (8 %), kidneys (3 %) and brain (3 %).

Absorbed selenocysteine, selenate, and selenite are available for the synthesis of selenoproteins (EFSA 2014). Cellular selenoprotein synthesis involves the degradation of free selenocysteine to selenide, which is then converted to selenophosphate and selenocysteine-tRNA[ser]sec before integration of selenocysteine into the expanding polypeptide chain. Utilisation of selenate or selenite for selenoprotein synthesis first requires reduction to selenide via interaction with glutathione. SEPP1 appears to play a central role in selenium supply to tissues and to participate in the regulation of selenium metabolism. Whole-body selenium appears to be regulated in the liver through the distribution from the functional selenium body pool between pathways of selenoprotein synthesis, including SEPP1, and selenium excretory metabolites.

Methylated selenium metabolites in the liver are predominantly excreted in urine, between 40 – 60% of total dietary intake (EFSA 2014). Urinary metabolites include a methylated selenosugar, Se-methyl-*N*-acetylgalactosamine, which is the major selenium compound in urine under normal dietary intakes. Under conditions of excessive selenium intake, the major elimination metabolite in urine is the trimethylselenonium ion, which is often accompanied by garlic breath (dimethylselenide). Unabsorbed selenium and some endogenous excretion from the turnover of intestinal mucosal cells, is excreted via the faeces (typically around 30% of total dietary intake). Selenium is also found in breast milk (EFSA 2014).

#### Short- and Long-term Exposures

Most evidence for the systemic toxicity of selenium and its compounds comes from epidemiological and animal studies, where the principal route of exposure was ingestion (ATSDR 2003, EA 2009, IPCS 1987). This section focuses on the limited evidence for local respiratory effects after inhalation (see Route-to-Route Extrapolation for a further discussion of oral exposure). As a general observation, IPCS (1987) observed that elemental selenium did not appear to be as toxic as either hydrogen selenide or selenium dioxide. Organic forms such as dimethylselenide are relatively non-toxic.

ATSDR (2003) found no case reports of death from inhalation of selenium dust and its compounds. In animals, the acute lethality of inhaled elemental selenium dust and selenium dioxide has been investigated. No deaths were reported in rabbits or guinea pigs exposed to dust at 31 mg/m3 for 4-hours per day, every other day for 8 days. Higher levels were not tested. All rats exposed to 150 mg/m3 of selenium dioxide for up to 4 hours died, but those exposed to 90 mg/m3 survived (IPCS 1987). Morphological examination of the organs revealed that intra-alveolar and perivascular oedema occurred in the lungs, and haemorrhages and degenerative changes were found in the liver, kidney, and heart.

Workers in the production and recovery of selenium compounds and those in the manufacture of glass or rectifiers have been exposed to fumes and dusts of selenium and its compounds, mostly elemental selenium, and selenium dioxide (ATSDR 2003, IPCS 1987). Inhalation was expected to be the principal route of exposure. These studies showed that the respiratory tract is the primary target following inhalation, but gastrointestinal and cardiovascular, as well as irritation of the skin and eyes, also occurred. In addition, short-term animal studies also reported haematological and hepatic effects including hepatocellular degeneration and liver atrophy (IPCS 1987).

Selenium dioxide is volatile and is formed when selenium is heated in air and by the combustion of coal and other fossil fuels (de Groot 2009). It forms selenious acid on contact with water including perspiration and moist mucous membranes, which leads to irritation. Glover (1976) summarised the local and systemic toxicity of selenium dioxide via inhalation, primarily acute, but also possibly long-term effects. Acute local effects were seen in the lungs, gastric mucosa, skin, nails, and eyes. Sudden inhalation of large amounts produced pulmonary oedemas, due to a local irritant effect on lung alveoli (Glover 1970). Skin contact resulted in burns and/or dermatitis. "Rose eye", a pink discoloration of the skin of the eyelids, which often become puffy, was also sometimes reported. Reported systemic effects of selenium dioxide exposure included garlicky-smelling breath, metallic taste on the tongue, and indefinite socio-psychological effects such as lassitude and irritability. Garlicky breath was the first and most characteristic sign and had been used by occupational hygienists as a way of monitoring exposure. Glover (1967) studied a group of selenium workers in a rectifier factory between 1953 and 1956. A strong odour of garlic on the breath was detected in most workers with selenium-urinary levels of 0.5 - 1.0 mg/l, but not below these levels. Bronchial spasms, symptoms of asphyxiation, and persistent bronchitis were noted in workers briefly exposed to high concentrations (Wilson 1962 cited in ATSDR 2003).

In animal studies, rats exposed to selenium dust (average particle diameter, 1.2 μm) at levels of 33 mg/m3 for 8-hours, experienced severe respiratory effects including haemorrhage and oedema of the lungs, and several animals died (Hall et al. 1951). Histopathological examination of surviving animals revealed chronic interstitial pneumonitis. Acute exposure of rabbits and guinea pigs to selenium dust (average particle diameter, 1.2 μm) at a concentration of 33 mg/m3 resulted in mild interstitial pneumonitis or congestion, and slight emphysema in both species. Other histological findings included vascular lymphocytic infiltration and intra-alveolar foci of large macrophages. Cardiovascular effects were not observed at the same concentration in rabbits or guinea pigs.

Hepatoxicity, slight liver congestion and mild centrilobular atrophy, was observed in rats one month after an 8-hour exposure to selenium dust at 33 mg/m3 (Hall et al. 1951). Three weeks following acute exposure to elemental selenium dust at a level of 33 mg/m3 for 4-hours every other day for 8 days, 4/10 guinea pigs exhibited slight hepatic congestion with mild central atrophy and 2/10 showed some fatty hepatocellular degeneration (Dudley and Miller 1941). The kidneys did not appear to be affected in guinea pigs (Dudley and Miller 1941, Hall et al. 1951) after acute inhalation exposure to 8 mg/m3 for 4 hours.

No histopathological changes in the adrenal gland were observed in rats exposed to elemental selenium dust at 33 mg/m3 for 8 hours (Hall et al. 1951). Histopathological changes in the spleen were not observed in guinea pigs exposed to dust (average particle diameter, 1.2 μm) at 33 mg/m3 for 8-hours (Hall et al. 1951). Injury to the spleen was observed in guinea pigs following exposure for 4 hours, every other day, for 8-days to dust at a level of 33 mg/m3. Specific effects included congestion of the spleen, fissuring red pulp, and increased polymorphonuclear leukocytes.

No studies of reproductive and developmental toxicity were found (ATSDR 2003).

Workers exposed over a long period of time to elemental selenium and selenium dioxide aerosols, between 0.35 – 24.8 mg/m3 and 0.11 – 0.78 mg/m3, respectively, developed rhinitis, nasal bleeding, headaches, weight loss, irritability, and pain in their extremities (Izraelson et al. 1973 cited by IPCS 1987). In another study in a rectifier factory, with reported selenium dioxide concentrations of 0.007 – 0.05 mg selenium/m3, more than 50% of the 62 workers investigated complained of irritability, sleeplessness, loss of appetite and nausea (Kinnigkeit 1962 cited in ATSDR 2003). Clinical examination revealed irritation of the mucosa in 9 of 62 exposed workers with conjunctivitis and slight tracheobronchitis. In the highest exposed group, those involved in the electrical testing of rectifier plates, abnormal results from the Takata reaction and thymol test suggested impaired liver function. Chronic exposure of 40 workers at a copper refinery produced increased nose irritation and sputum (Holness et al. 1989 cited in ATSDR 2003). The exact concentration of selenium was not given, but the concentration was reported to exceed 0.2 mg selenium/m3. Confounding variables in this study include concurrent exposure to several other metals including copper, nickel, silver, lead, arsenic, and tellurium. In a sub-chronic repeat dose study, rats were exposed to selenium dioxide at 3 – 5 mg/m3, 6 – 9 mg/m3, or 10 – 30 mg/m3, for 6 hours per day, every other day for a month (Filatova 1951 cited by IPCS 1987). Severe mortality was observed at doses greater than 6 to 9 mg/m3, but all rats survived in the lowest dose group (3 to 5 mg/m3). Histological examination of the rats in the lowest dose group revealed degenerative changes in the liver, renal tubules, dystrophy of heart muscle, hyperaemia, and hypertrophy of the splenic pulp. In the higher dose groups, severe weight loss was observed during the final two weeks of the experiment leading to death. Similar histopathological changes were observed compared to the lowest dose group, although the effects were much more pronounced. At the highest tested dose (greater than 10 mg/m3), the rats showed respiratory distress and anaemia with lung oedemas similar to those seen under conditions of acute exposure. Rabbits exposed to 20 mg/m3 selenium dioxide or 40 mg/m3 elemental selenium for 2 hours per day for 5 days showed a decrease in blood catalase activity (Lipinskij 1962 cited by IPCS 1987). In another study, rabbits exposed to 20 mg/m3 for 2 hours per day for 12 weeks had decreased total and reduced glutathione levels, but there was no observed change in oxidised glutathione levels.

#### Pivotal Studies

Many of the pivotal studies cited by ATSDR (2003) and IPCS (1987) are in German or Russian and the details have not been translated for this summary.

In the study by Hall et al. (1951), rats were exposed to the fume produced by vacuum evaporation **evaporation** of selenium **selenium** metal (average particle diameter, 1.2 μm) at a level of 33 mg/m3 for 8-hours and experienced severe respiratory effects, with 10% mortality. After the animals **animals** were killed the lungs **lungs** showed a mild or moderately severe pneumonitis. **pneumonitis.** The possibility that the changes were due to contamination by traces of selenium oxide cannot be excluded. The acute exposure of guinea pigs **guineapigs** and rabbits **rabbits** to selenium dust of average particle size of 1.2 µm, and a concentration of about 30 mg/m3 for 16-hours resulted in mild interstitial pneumonitis and slight emphysema with no significant changes in other organs when assessed at varying periods up to one month after exposure. Intraperitoneal injection of selenium suspension and application of a paste to the shaved skin produced no pathological change.

#### Genotoxicity and Carcinogenicity

Selenium and its inorganic compounds have both genotoxic and anti-genotoxic effects with the latter generally occurring at lower concentrations (ATSDR 2003). Selenium dioxide was found to be mutagenic in both the Ames and the VITO-TOX *Salmonella typhimurium* tests of genotoxicity.

In general, sodium selenite and sodium selenate produced mixed results in bacterial mutagenicity test systems (ATSDR 2003). The addition of glutathione to test mixtures enhanced the genotoxicity of sodium selenite, sodium selenate, and sodium selenide in bacterial test systems, indicating that production of a reactive species mutagenic for bacteria occurred via a reductive mechanism following concomitant exposure to these compounds (Whiting et al. 1980). This finding was supported by results in mammalian test systems (ATSDR 2003).

Overall, the results with mammalian cell systems were also mixed, although sodium selenite is more consistently genotoxic in these systems (ATSDR 2003). Results of *in vivo* genotoxicity tests were also largely negative (EVM 2003), except where there was overt toxicity.

ATSDR (2003) found no epidemiological data that supported a causal association between inhalation of selenium and its compounds and human cancers. No studies were identified regarding the carcinogenicity of selenium in laboratory animals after inhalation exposure.

### Short-term Exposure

No authoritative HBGV for selenium and its compounds were identified to protect public health.

### Long-term Exposure

The industry REACH dossiers have proposed long-term inhalation HBGV for selenium and its compounds to protect public health. These DNEL are all based on route-to-route extrapolation from systemic effects observed after excessive dietary (oral) exposure. See section on ‘Route-to-Route Extrapolation’ for a further discussion of systemic effects via oral exposure.

#### REACH Chemical Dossiers for Selenium and its compounds

The industry REACH dossiers for selenium, selenium dioxide, sodium selenate, and sodium selenite on the ECHA dissemination portal[[10]](#footnote-11),[[11]](#footnote-12),[[12]](#footnote-13),[[13]](#footnote-14) were reviewed. In all cases, the DNEL for chronic exposures to protect the general population was based on an upper limit of total intake of 0.3 mg selenium/day proposed by SCF (2000) from a study of selenosis in the Chinese population (Yang and Zhou 1994). The POD was the NOAEL of 0.9 mg selenium/day, identified by Yang et al. (1989a and 1989b). As the Yang et al. studies utilised biomonitoring data, a total UF of 3 was considered appropriate as the toxicokinetic factor of intraspecies variation had already been accounted for. This yielded an oral HBGV of 0.3 mg selenium/day, which was converted to an air concentration by assuming a normalised adult body weight of 70 kg and a daily adult inhalation rate of 20 m3 air, and then corrected for the differences in molecular weight for each compound compared with elemental selenium.

The recommended DNELs were 0.015 mg/m3 for selenium (no molecular weight multiplier), 0.021 mg/m3 for selenium dioxide (molecular weight multiplier of 1.4), 0.036 mg/m3 for sodium selenate (molecular weight multiplier of 2.39), and 0.033 mg/m3 for sodium selenite (molecular weight multiplier of 2.19).

### Route-to-Route Extrapolation

Most authoritative reviews have focused on the systemic toxicity of selenium and the symptoms of selenosis as observed via dietary (oral) exposures (ATSDR 2003, EVM 2003, EA 2009, US EPA 1991, SCF 2000, and WHO 2011). Most oral HBGVs are based on the studies of selenosis arising in the Chinese population following excessive dietary intakes (Yang et al. 1989a and 1989b, Yang and Zhou 1994) and are summarised below. They have been corrected to a 70 kg bodyweight for comparison purposes.

|  |  |  |  |
| --- | --- | --- | --- |
| **Summary of HBGV for Long-term Dietary Exposures** | | | |
| **Guideline** | **Value (mg/kg/day)** | **Critical effect(s)** | **Pivotal reference(s)** | |
| ATSDR chronic MRL | 0.35 | Selenosis | Yang and Zhou 1994 | |
| EA TDI | 0.44 | Selenosis | EVM 2003 | |
| EVM Safe Upper Level | 0.45 | Selenosis | Yang et al. 1989a and 1989b | |
| US EPA RfD \*\*\* | 0.35 | Selenosis | Yang et al. 1989a and 1989b | |
| WHO Drinking water guideline (NOAEL used for derivation) | 0.40 | Selenosis | WHO 2011 | |
| SCF tolerable upper intake level (UL) | 0.30 | Selenosis | SCF 2000; EFSA 2014 | |
| \* Converted from chronic Minimal Risk Level (MRL) of 0.005 mg/kg bw/day assuming a 70 kg bodyweight.  \*\* Converted from tolerable daily intake (TDI) of 0.0064 mg/kg bw/day assuming a 70 kg bodyweight.  \*\*\* Converted from Reference Dose (RfD) of 0.005 mg/kg bw/day assuming a 70 kg bodyweight. | | | | |

### Summary

Little of the available evidence on health effects via inhalation is suitable for the derivation of an HBGV (ATSDR 2003, IPCS 1987) for local acute or repeat dose toxicity.

In general, IPCS (1987) concluded that industrial inhalation exposures had not been adequately characterised and there was a need for further studies to be conducted. They found that exposures were poorly characterised and there was a general lack of any follow-up work or use of a control group. The physical and chemical form of selenium varied which undoubtedly influenced the findings. IPCS also expressed a note of caution in the interpretation of animal studies to characterise the toxicity of selenium and its compounds in workers and the general population. Firstly, the database was limited. Secondly, the air concentrations and exposure durations of the general population (where exposures were lower, but of a much longer duration) were often quite different from those found in the workplace.

No short-term HBGV were found for selenium and its compounds to protect public health.

Long term HBGV for inhalation exposure were derived in the industry REACH dossiers for selenium, selenium dioxide, selenium selenate, and selenium selenite. They are all based on an upper limit of total selenium intake of 0.3 mg/day from studies of selenosis from excessive dietary exposures (SCF 2000, Yang and Zhou 1994) by route-to-route extrapolation. After correction to an air concentration, the individual DNEL values differ only by the relative molecular weight of the different compounds.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Summary of HBGV for Long-term Inhalation Exposures** | | | | |
| **Guideline** | **Value (mg/m3)** | **Duration** | **Critical effect(s)** | **Pivotal reference(s)** |
| Current EAL | 0.001 | Annual | - | OEL 2011 |
| DNEL (selenium) | 0.015 | Lifetime | Selenosis | Yang and Zhou 1994 |
| DNEL (selenium dioxide) | 0.021 | Lifetime | Selenosis | Yang and Zhou 1994 |
| DNEL (sodium selenate) | 0.036 | Lifetime | Selenosis | Yang and Zhou 1994 |
| DNEL (sodium selenite) | 0.033 | Lifetime | Selenosis | Yang and Zhou 1994 |
|  | | | | |

### Recommendations

#### Short-term EAL

It is not proposed to establish a short-term EAL for selenium and its compounds because of insufficient evidence.

#### Long-term EAL

A long-term EAL of 0.002 mg/m3 as a 24-hour mean is recommended to protect the public. It is based on route-to-route extrapolation from the systemic effect of selenosis via excessive dietary exposure. Several authoritative bodies (ATSDR 2003, EVM 2003, SCF 2000, US EPA 1991, WHO 2011) have derived oral HBGV for the protection of the public in the range 0.3 – 0.45 mg/day, which corresponds to an air concentration between 0.015 – 0.023 mg/m3 (assuming an adult inhalation rate of 20 m3/day). Rounding the values in this range to one significant figure yields an inhalation HBGV of 0.02 mg/m3. In deriving the long-term EAL, it is also appropriate to allocate a significant proportion of the HBGV to the diet, which is the predominant route of exposure. The long-term EAL assumes an allocation of 10% of the HBGV to air, which is similar to the allocation for drinking water by WHO (2011). No additional UF is required.

The long-term EAL provides a margin of safety (from approximately 3 to >1,000) for local respiratory and irritant effects observed in acute and chronic occupational and animal studies after inhalation of selenium and its compounds (see earlier summary of the evidence for effects by inhalation).

### Abbreviations and Definitions

|  |  |
| --- | --- |
| ATSDR | Agency for Toxic Substances and Disease Registry |
| DNEL | Derived No-Effect Level is defined as the level of exposure to a substance above which humans should not be exposed. DNEL apply to health effects with a threshold. |
| EA | Environment Agency |
| EAL | Environmental Assessment Level |
| ECHA | European Chemicals Agency |
| EFSA | European Food Safety Authority |
| EVM | Expert Group on Vitamins and Minerals |
| HBGV | Health-Based Guidance Value |
| IPCS | International Programme on Chemical Safety, World Health Organization |
| MRL | Minimal Risk Level is defined as an estimate of the amount of a chemical a person can eat, drink, or breathe each day without a detectable risk to health. MRL values are developed for health effects other than cancer. |
| NOAEL | No Observed Adverse Effect Level |
| OEL | Occupational Exposure Limit |
| POD | Point of Departure |
| RfC | Reference Concentration in air |
| SCF | Scientific Committee on Food (now disbanded and replaced by EFSA) |
| SEPP1 | Selenoprotein P (SEPP1), encoded by the SEPP1 gene, is the main mechanism for transportation of selenium from the liver to other parts of the human body |
| UF | Uncertainty Factor |
| US EPA | United States Environmental Protection Agency |
| WHO | World Health Organization |

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### Abbreviations and Definitions

|  |  |
| --- | --- |
| ADI | Acceptable Daily Intake |
| AICIS | Australian Industrial Chemicals Introduction Scheme |
| CAS | Chemical Abstract Service |
| CLP | Classification, Labelling and Packaging |
| CVMP | EU Committee for Veterinary Medicinal Products |
| DNEL | Derived No Effect Level is defined as the level of exposure to a substance above which humans should not be exposed. DNEL apply to health effects with a threshold. |
| DNP | Di-nitroso derivative N,N'-dinitrosopiperazine |
| DNZP | N,N'-dinitrosopiperazine |
| EAL | Environmental Assessment Level |
| ECB | European Chemical Bureau |
| ECHA | European Chemicals Agency |
| EFSA | European Food Safety Authority | |
| EMEA | European Agency for the Evaluation of Medical products |
| EU | European Union |
| GD | Gestation day |
| HSDB | Hazardous Substances Data Bank |
| HSE | Health and Safety Executive |
| HBGV | Health-Based Guidance Value |
| IARC | International Agency for Research on Cancer |
| LC50 | Lethal Concentration that kills 50 % of exposed animals in a study |
| LOAEC/L | Lowest Observable Adverse Effect Concentration or Level |
| LOEL | Lowest Observable Effect Level |
| NOAEC/L | No Observed Adverse Effect Concentration or Level |
| NOEL | No Observed Effect Level |
| NDMA | N-nitrosodimethylamine | |
| NPIP | N-nitrosopiperidine | |
| NPZ | N-mononitrosopiperazine |
| OECD | Organisation for Economic Co-operation and Development |
| OEL | Occupational Exposure Level are broadly defined as a measurable concentration of a substance in air that represents a point of reference for the development of workplace strategies to protect workers from health risks associated with inhalation of chemical substances. |
| POD | Point of Departure |
| ppm | Parts Per Million |
| EU REACH | Registration, Evaluation, Authorisation and Restriction of Chemicals |
| SCCS | Scientific Committee on Consumer Safety – European Commission |
| SECO | Simple European Calculator | |
| sRV | Standard respiratory volume | |
| TD50 | Dose resulting in a 50% tumour incidence over background | |
| WEL | Workplace exposure limit |

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1. PZ was used as an active ingredient in human medicines, although has been disused in most developed countries. This was primarily because of concerns about possible carcinogenicity and electroencephalographic changes (ECB 2005). [↑](#footnote-ref-2)
2. Bellander et al. (1987) cited by ECB (2005) reported PZ levels in urine as ranging from 70 to 4,700 µg per person per 24-hour period, which differs slightly from the later figures reported by Bellander et al. (1988a). [↑](#footnote-ref-3)
3. ECB (2005) were not explicit about the reason for the estimate of 1% or why they considered it conservative. One possible reason may have been the lower estimated conversion rate of 0.01%, which had been estimated from the earlier study by Bellander et al. (1985 cited by ECB 2005). However, they concluded that using this estimate resulted in a reasonable agreement with the results reported by Bellander et al. (1988a). [↑](#footnote-ref-4)
4. Bellander et al. (1988b) did not provide a reference for the relationship between the urinary level of NPZ and the total amount of NPZ formed by the body. ECB (2005) cited the later work of Tricker et al. (1991 cited by ECB 2005), which reported the observed excretion rate was about 10% (that is, 10% of the total amount of NPZ formed was excreted in urine). Using the inferred relationship between the highest excreted amount (1.7 µg MNPZ per person) and the total amount formed in the body (50 µg MNPZ per person) by Bellander et al. (1988b), an assumed excretion rate of 3.4% (1.7/50 x 100) can be estimated, which was about one third of the rate reported by Tricker et al. (1991 cited by ECB 2005). Applying an excretion rate of 10% (as proposed by ECB 2005), results in a total amount of 17 µg NPZ/person at the maximum excreted concentration of 1.7 µg NPZ/person as observed in Bellander et al. (1988b). This corresponds to a PZ to NPZ conversion rate of 1.5% [(17 µg NPZ/1100 µg PZ) \* 100]. [↑](#footnote-ref-5)
5. AICIS cited an unnamed study (1987) from the EU REACH dossier (ECHA 2023). However, the chemical name and CAS No. stated in AICIS (2020) is PZ dihydrogen phosphate 14538-56-8 whereas the chemical name and CAS No. stated in the EU REACH dossier is PZ phosphate CAS 1951-97-9. [↑](#footnote-ref-6)
6. Using US EPA BMDS, 2.7 mg/kg bw/day is the Bayesian model average BMDL10. [↑](#footnote-ref-7)
7. <https://echa.europa.eu/registration-dossier/-/registered-dossier/15182> [↑](#footnote-ref-8)
8. The short-term (15-minute reference period) Workplace exposure limit (WEL) published by HSE (2020) is 0.3 mg/m3. WELs are GB occupational exposure limits (OELs) approved by the Health and Safety Executive. [↑](#footnote-ref-9)
9. In this case, excessive dietary exposure is approximately 0.02 mg/kg/day, or 10–20 times higher than normal daily intake. [↑](#footnote-ref-10)
10. <https://echa.europa.eu/registration-dossier/-/registered-dossier/15204/7/1> [↑](#footnote-ref-11)
11. <https://echa.europa.eu/registration-dossier/-/registered-dossier/11470/7/1> [↑](#footnote-ref-12)
12. <https://echa.europa.eu/registration-dossier/-/registered-dossier/25874/7/1> [↑](#footnote-ref-13)
13. <https://echa.europa.eu/registration-dossier/-/registered-dossier/11204/7/1> [↑](#footnote-ref-14)