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ICH guideline Q3D on elemental impurities

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Document History

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Q3D	Post sign-off corrigendum in: Table 4.1 W and Al were removed from the list of included elemental impurities in Class 2B and 3 respectively. Table A.2.1 the Class for Ni was changed to read 3 instead of 2.	14 June 2013
Q3D	Post sign-off minor editorial corrections including: removal of references to Appendix 5 (pgs i & 13); deletion of redundant text (pg 4); change of Option 2 to Option 2a (pg 10); insertion of omitted text under Safety Limiting Toxicity (pg 35); removal of duplicated redundant text (pg 41); replacing references to "metals" in text and "metal" in Table A.4.7 title with "elementals" and "elements" (pg 73); and deletion of header Table A.4.10 (pg 75).	26 July 2013
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Current *Step 4* version

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Q3D	Corrigendum to correct: the modifying factor in the text of the safety assessment for Selenium (changed to 2 instead of 10 consistent with Section 3.1); and two references for consistency in the safety assessments for Barium (deleted reference) and Vanadium (revised reference).	16 December 2014

ICH Harmonised Guideline

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on 12 November 2014, this guideline is recommended for adoption
to the regulatory parties to ICH

ICH guideline Q3D on elemental impurities

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1. Introduction

Elemental impurities in drug products may arise from several sources; they may be residual catalysts that were added intentionally in synthesis or may be present as impurities (e.g., through interactions with processing equipment or container/closure systems or by being present in components of the drug product). Because elemental impurities do not provide any therapeutic benefit to the patient, their levels in the drug product should be controlled within acceptable limits. There are three parts of this guideline: the evaluation of the toxicity data for potential elemental impurities; the establishment of a Permitted Daily Exposure (PDE) for each element of toxicological concern; and application of a risk-based approach to control elemental impurities in drug products. An applicant is not expected to tighten the limits based on process capability, provided that the elemental impurities in drug products do not exceed the PDEs. The PDEs established in this guideline are considered to be protective of public health for all patient populations. In some cases, lower levels of elemental impurities may be warranted when levels below toxicity thresholds have been shown to have an impact on other quality attributes of the drug product (e.g., element catalyzed degradation of drug substances). In addition, for elements with high PDEs, other limits may have to be considered from a pharmaceutical quality perspective and other guidelines should be consulted (e.g., ICH Q3A).

This guideline presents a process to assess and control elemental impurities in the drug product using the principles of risk management as described in ICH Q9. This process provides a platform for developing a risk-based control strategy to limit elemental impurities in the drug product.

2. Scope

The guideline applies to new finished drug products (as defined in ICH Q6A and Q6B) and new drug products containing existing drug substances. The drug products containing purified proteins and polypeptides (including proteins and polypeptides produced from recombinant or non-recombinant origins), their derivatives, and products of which they are components (e.g., conjugates) are within the scope of this guideline, as are drug products containing synthetically produced polypeptides, polynucleotides, and oligosaccharides.

This guideline does not apply to herbal products, radiopharmaceuticals, vaccines, cell metabolites, DNA products, allergenic extracts, cells, whole blood, cellular blood components or blood derivatives including plasma and plasma derivatives, dialysate solutions not intended for systemic circulation, and elements that are intentionally included in the drug product for therapeutic benefit. This guideline does not apply to products based on genes (gene therapy), cells (cell therapy) and tissue (tissue engineering). In some regions, these products are known as advanced therapy medicinal products.

This guideline does not apply to drug products used during clinical research stages of development. As the commercial process is developed, the principles contained in this guideline can be useful in evaluating elemental impurities that may be present in a new drug product.

Application of Q3D to existing products is not expected prior to 36 months after publication of the guideline by ICH.

3. Safety assessment of potential elemental impurities

3.1. Principles of the safety assessment of elemental impurities for oral, parenteral and inhalation routes of administration

The method used for establishing the PDE for each elemental impurity is discussed in detail in Appendix 1. Elements evaluated in this guideline were assessed by reviewing the publicly available data contained in scientific journals, government research reports and studies, international regulatory standards (applicable to drug products) and guidance, and regulatory authority research and assessment reports. This process follows the principles described in ICH Q3C: Residual Solvents. The available information was reviewed to establish the oral, parenteral and inhalation PDEs. For practical purposes, the PDEs to be applied to the drug product that are presented in Appendix 2 Table A.2.1 have been rounded to 1 or 2 significant figures.

A summary safety assessment identifying the critical study for setting a PDE for each element is included in Appendix 3. There are insufficient data to set PDEs by any route of administration for iridium, osmium, rhodium, and ruthenium. The PDEs for these elements were established on the basis of their similarity to palladium.

The factors considered in the safety assessment for establishing the PDE are listed below in approximate order of relevance:

- The likely oxidation state of the element in the drug product;
- Human exposure and safety data when it provided applicable information;
- The most relevant animal study;
- Route of administration;
- The relevant endpoint(s).

Standards for daily intake for some of the elemental impurities discussed in this guideline exist for food, water, air, and occupational exposure. Where appropriate, these standards were considered in the safety assessment and establishment of the PDEs.

The longest duration animal study was generally used to establish the PDE. When a shorter duration animal study was considered the most relevant, the rationale was provided in the individual safety assessment.

Inhalation studies using soluble salts (when available) were preferred over studies using particulates for inhalation safety assessment and derivation of inhalation PDEs. Depending on available data, inhalation PDEs were based on either local (respiratory system) or systemic toxicity. For PDEs established for inhalation (and oral or parenteral routes as applicable), doses were normalized to a 24-hour, 7-day exposure.

In the absence of data and/or where data are available but not considered sufficient for a safety assessment for the parenteral and or inhalation route of administration, modifying factors based on oral bioavailability were used to derive the PDE from the oral PDE:

- Oral bioavailability <1%: divide by a modifying factor of 100;
- Oral bioavailability ≥ 1% and <50%: divide by a modifying factor of 10;
- Oral bioavailability ≥50% and <90%: divide by a modifying factor of 2; and

- Oral bioavailability ≥ 90%: divide by a modifying factor of 1.

Where oral bioavailability data or occupational inhalation exposure limits were not available, a calculated PDE was used based on the oral PDE divided by a modifying factor of 100 (Ref. 1).

3.2. Other routes of administration

PDEs were established for oral, parenteral and inhalation routes of administration. When PDEs are necessary for other routes of administration, the concepts described in this guideline may be used to derive PDEs. An assessment may either increase or decrease an established PDE. The process of derivation of the PDE for another route of administration may include the following:

- Consider the oral PDE in Appendix 3 as a starting point in developing a route-specific PDE. Based on a scientific evaluation, the parenteral and inhalation PDEs may be a more appropriate starting point.
- Assess if the elemental impurity is expected to have local effects when administered by the intended route of administration:
  - If local effects are expected, assess whether a modification to an established PDE is necessary.
  - Consider the doses/exposures at which these effects can be expected relative to the adverse effect that was used to set an established PDE.
  - If local effects are not expected, no adjustment to an established PDE is necessary.
- If available, evaluate the bioavailability of the element *via* the intended route of administration and compare this to the bioavailability of the element by the route with an established PDE:
  - When a difference is observed, a correction factor may be applied to an established PDE. For example, when no local effects are expected, if the oral bioavailability of an element is 50% and the bioavailability of an element by the intended route is 10%, a correction factor of 5 may be applied.
- If a PDE proposed for the new route is increased relative to an established PDE, quality attributes may need to be considered.

3.3. Justification for elemental impurity levels higher than an established PDE

Levels of elemental impurities higher than an established PDE (see Table A.2.1) may be acceptable in certain cases. These cases could include, but are not limited to, the following situations:

- Intermittent dosing;
- Short term dosing (i.e., 30 days or less);
- Specific indications (e.g., life-threatening, unmet medical needs, rare diseases).

Examples of justifying an increased level of an elemental impurity using a subfactor approach of a modifying factor (Ref. 2,3) are provided below. Other approaches may also be used to justify an increased level. Any proposed level higher than an established PDE should be justified on a case-by-case basis.

Example 1: element X is present in an oral drug product. From the element X monograph in Appendix 3, a No-Observed-Adverse-Effect Level (NOAEL) of 1.1 mg/kg/day was identified. Modifying factors

F1-F5 have been established as 5, 10, 5, 1 and 1, respectively. Using the standard approach for modifying factors as described in Appendix 1, the PDE is calculated as follows:

PDE = 1.1 mg/kg/d x 50 kg / 5 x 10 x 5 x 1 x 1 = 220 µg/day

Modifying factor F2 (default = 10) can be subdivided into two subfactors, one for toxicokinetics (TK) and one for toxicodynamics, each with a range from 1 to 3.16. Using the plasma half-life of 5 days, the TK adjustment factor could be decreased to 1.58 for once weekly administration (~1 half-life), and to 1 for administration once a month (~5 half-lives). Using the subfactor approach for F2, the proposed level for element X administered once weekly can be calculated as follows:

Proposed level = 1.1 mg/kg/d x 50 kg / 5 x (1.6 x 3.16) x 5 x 1 x 1 = 440 µg/day

For practical purposes, this value is rounded to 400 µg/day.

Example 2: The TK adjustment factor approach may also be appropriate for elemental impurities that were not developed using the modifying factor approach. For element Z, a Minimal Risk Level (MRL) of 0.02 mg/kg/day was used to derive the oral PDE. From literature sources, the plasma half-life was reported to be 4 days. This element is an impurity in an oral drug product administered once every 3 weeks (~ 5 half-lives). Using first-order kinetics, the established PDE of 1000 µg/day is modified as follows:

Proposed level = 0.02 mg/kg/d x 50 kg / 1/3.16 = 3.16 mg/day

For practical purposes, this value is rounded to 3000 µg/day.

3.4. Parenteral products

Parenteral drug products with maximum daily volumes up to 2 liters may use the maximum daily volume to calculate permissible concentrations from PDEs. For products whose daily volumes, as specified by labeling and/or established by clinical practice, may exceed 2 liters (e.g., saline, dextrose, total parenteral nutrition, solutions for irrigation), a 2-liter volume may be used to calculate permissible concentrations from PDEs. (Ref. 4)

4. Element classification

The elements included in this guideline have been placed into three classes based on their toxicity (PDE) and likelihood of occurrence in the drug product. The likelihood of occurrence is derived from several factors including: probability of use in pharmaceutical processes, probability of being a co-isolated impurity with other elemental impurities in materials used in pharmaceutical processes, and the observed natural abundance and environmental distribution of the element. For the purposes of this guideline, an element with low natural abundance refers to an element with a reported natural abundance of $\leq$ 1 atom/10^6 atoms of silicon (Ref. 5). The classification scheme is intended to focus the risk assessment on those elements that are the most toxic but also have a reasonable probability of inclusion in the drug product (see Table 5.1). The elemental impurity classes are:

Class 1: The elements, As, Cd, Hg, and Pb, are human toxicants that have limited or no use in the manufacture of pharmaceuticals. Their presence in drug products typically comes from commonly used materials (e.g., mined excipients). Because of their unique nature, these four elements require evaluation during the risk assessment, across all potential sources of elemental impurities and routes of administration. The outcome of the risk assessment will determine those components that may require additional controls which may in some cases include testing for Class 1 elements. It is not expected that all components will require testing for Class 1 elemental impurities; testing should only

be applied when the risk assessment identifies it as the appropriate control to ensure that the PDE will be met.

Class 2: Elements in this class are generally considered as route-dependent human toxicants. Class 2 elements are further divided in sub-classes 2A and 2B based on their relative likelihood of occurrence in the drug product.

- **Class 2A** elements have relatively high probability of occurrence in the drug product and thus require risk assessment across all potential sources of elemental impurities and routes of administration (as indicated). The class 2A elements are: Co, Ni and V.
- **Class 2B** elements have a reduced probability of occurrence in the drug product related to their low abundance and low potential to be co-isolated with other materials. As a result, they may be excluded from the risk assessment unless they are intentionally added during the manufacture of drug substances, excipients or other components of the drug product. The elemental impurities in class 2B include: Ag, Au, Ir, Os, Pd, Pt, Rh, Ru, Se and Tl.

Class 3: The elements in this class have relatively low toxicities by the oral route of administration (high PDEs, generally > 500 µg/day) but may require consideration in the risk assessment for inhalation and parenteral routes. For oral routes of administration, unless these elements are intentionally added, they do not need to be considered during the risk assessment. For parenteral and inhalation products, the potential for inclusion of these elemental impurities should be evaluated during the risk assessment, unless the route specific PDE is above 500 µg/day. The elements in this class include: Ba, Cr, Cu, Li, Mo, Sb, and Sn.

Other elements: Some elemental impurities for which PDEs have not been established due to their low inherent toxicity and/or differences in regional regulations are not addressed in this guideline. If these elemental impurities are present or included in the drug product they are addressed by other guidelines and/or regional regulations and practices that may be applicable for particular elements (e.g., Al for compromised renal function; Mn and Zn for patients with compromised hepatic function), or quality considerations (e.g., presence of W impurities in therapeutic proteins) for the final drug product. Some of the elements considered include: Al, B, Ca, Fe, K, Mg, Mn, Na, W and Zn.

5. Risk assessment and control of elemental impurities

In developing controls for elemental impurities in drug products, the principles of quality risk management, described in ICH Q9, should be considered. The risk assessment should be based on scientific knowledge and principles. It should link to safety considerations for patients with an understanding of the product and its manufacturing process (ICH Q8 and Q11). In the case of elemental impurities, the product risk assessment would therefore be focused on assessing the levels of elemental impurities in a drug product in relation to the PDEs presented in this guidance. Information for this risk assessment includes but is not limited to: data generated by the applicant, information supplied by drug substance and/or excipient manufacturers and/or data available in published literature.

The applicant should document the risk assessment and control approaches in an appropriate manner. The level of effort and formality of the risk assessment should be proportional to the level of risk. It is neither always appropriate nor always necessary to use a formal risk management process (using recognized tools and/or formal procedures, e.g., standard operating procedures.) The use of informal risk management processes (using empirical tools and/or internal procedures) may also be considered

acceptable. Tools to assist in the risk assessment are described in ICH Q8 and Q9 and will not be presented in this guideline.

5.1. General principles

For the purposes of this guideline, the risk assessment process can be described in three steps:

- Identify known and potential sources of elemental impurities that may find their way into the drug product.
- Evaluate the presence of a particular elemental impurity in the drug product by determining the observed or predicted level of the impurity and comparing with the established PDE.
- Summarize and document the risk assessment. Identify if controls built into the process are sufficient or identify additional controls to be considered to limit elemental impurities in the drug product.

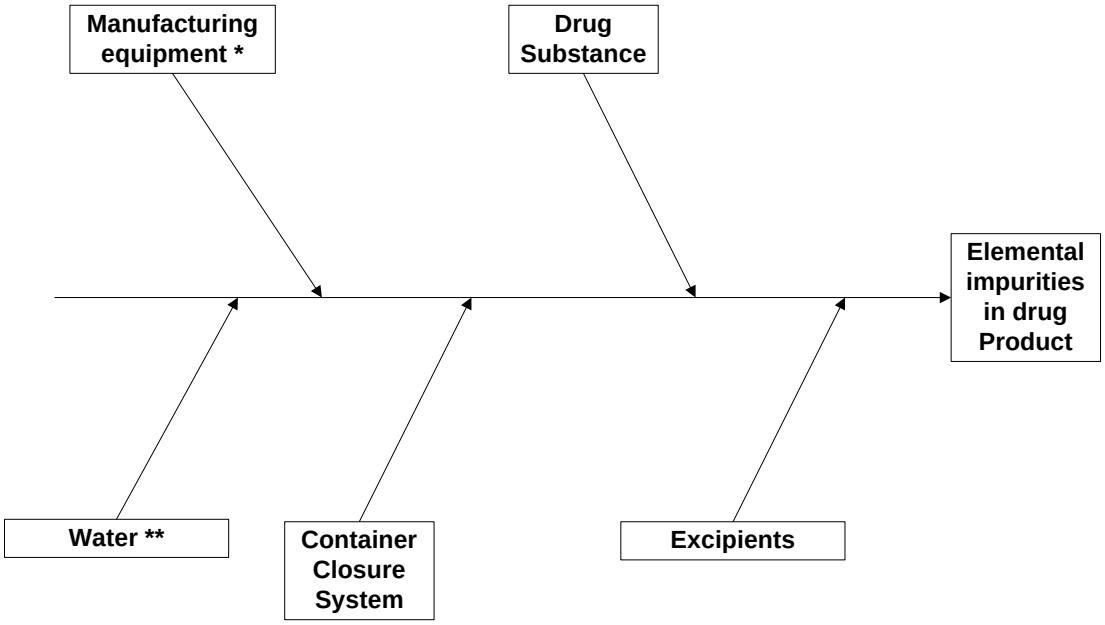
In many cases, the steps are considered simultaneously. The outcome of the risk assessment may be the result of iterations to develop a final approach to ensure the potential elemental impurities do not exceed the PDE.

5.2. Potential sources of elemental impurities

In considering the production of a drug product, there are broad categories of potential sources of elemental impurities.

- Residual impurities resulting from elements intentionally added (e.g., catalysts) in the formation of the drug substance, excipients or other drug product components. The risk assessment of the drug substance should address the potential for inclusion of elemental impurities in the drug product.
- Elemental impurities that are not intentionally added and are potentially present in the drug substance, water or excipients used in the preparation of the drug product.
- Elemental impurities that are potentially introduced into the drug substance and/or drug product from manufacturing equipment.
- Elemental impurities that have the potential to be leached into the drug substance and drug product from container closure systems.

The following diagram shows an example of typical materials, equipment and components used in the production of a drug product. Each of these sources may contribute elemental impurities to the drug product, through any individual or any combination of the potential sources listed above. During the risk assessment, the potential contributions from each of these sources should be considered to determine the overall contribution of elemental impurities to the drug product.



* The risk of inclusion of elemental impurities can be reduced through process understanding, equipment selection, equipment qualification and Good Manufacturing Practice (GMP) processes.

** The risk of inclusion of elemental impurities from water can be reduced by complying with compendial (e.g., European Pharmacopoeia, Japanese Pharmacopoeia, US Pharmacopeial Convention) water quality requirements, if purified water or water for injection is used in the manufacturing process(es).

5.3. Identification of potential elemental impurities

Potential elemental impurities derived from intentionally added catalysts and inorganic reagents: If any element listed in Table 5.1 is intentionally added, it should be considered in the risk assessment. For this category, the identity of the potential impurities is known and techniques for controlling the elemental impurities are easily characterized and defined.

Potential elemental impurities that may be present in drug substances and/or excipients: While not intentionally added, some elemental impurities may be present in some drug substances and/or excipients. The possibility for inclusion of these elements in the drug product should be reflected in the risk assessment.

For the oral route of administration, the risk assessment should evaluate the possibility for inclusion of Class 1 and Class 2A elemental impurities in the drug product. For parenteral and inhalation routes of administration, the risk assessment should evaluate the possibility for inclusion of the Class 1, Class 2A and Class 3 elemental impurities as shown in Table 5.1.

Potential elemental impurities derived from manufacturing equipment: The contribution of elemental impurities from this source may be limited and the subset of elemental impurities that should be considered in the risk assessment will depend on the manufacturing equipment used in the production of the drug product. Application of process knowledge, selection of equipment, equipment qualification and GMP controls ensure a low contribution from manufacturing equipment. The specific elemental impurities of concern should be assessed based on knowledge of the composition of the components of the manufacturing equipment that come in contact with components of the drug

product. The risk assessment of this source of elemental impurities is one that can potentially be utilized for many drug products using similar process trains and processes.

In general, the processes used to prepare a given drug substance are considerably more aggressive than processes used in preparing the drug product when assessed relative to the potential to leach or remove elemental impurities from manufacturing equipment. Contributions of elemental impurities from drug product processing equipment would be expected to be lower than contributions observed for the drug substance. However, when this is not the case based on process knowledge or understanding, the applicant should consider the potential for incorporation of elemental impurities from the drug product manufacturing equipment in the risk assessment (e.g., hot melt extrusion).

Elemental impurities leached from container closure systems: The identification of potential elemental impurities that may be introduced from container closure systems should be based on a scientific understanding of likely interactions between a particular drug product type and its packaging. When a review of the materials of construction demonstrates that the container closure system does not contain elemental impurities, no additional risk assessment needs to be performed. It is recognized that the probability of elemental leaching into solid dosage forms is minimal and does not require further consideration in the risk assessment. For liquid and semi-solid dosage forms there is a higher probability that elemental impurities could leach from the container closure system during the shelf-life of the product. Studies to understand potential leachables from the container closure system (after washing, sterilization, irradiation, etc.) should be performed. This source of elemental impurities will typically be addressed during evaluation of the container closure system for the drug product.

Factors that should be considered (for liquid and semi-solid dosage forms) include but are not limited to:

- Hydrophilicity/hydrophobicity;
- Ionic content;
- pH;
- Temperature (cold chain *vs* room temperature and processing conditions);
- Contact surface area;
- Container/component composition;
- Terminal sterilization;
- Packaging process;
- Component sterilization;
- Duration of storage.

5.4. Recommendations for elements to be considered in the risk assessment

The following table provides recommendations for inclusion of elemental impurities in the risk assessment. This table can be applied to all sources of elemental impurities in the drug product.

Table 1. Elements to be Considered in the Risk Assessment

Element	Class	If intentionally added (all routes)	If not intentionally added		
			Oral	Parenteral	Inhalation
Cd	1	yes	yes	yes	yes
Pb	1	yes	yes	yes	yes
As	1	yes	yes	yes	yes
Hg	1	yes	yes	yes	yes
Co	2A	yes	yes	yes	yes
V	2A	yes	yes	yes	yes
Ni	2A	yes	yes	yes	yes
Tl	2B	yes	no	no	no
Au	2B	yes	no	no	no
Pd	2B	yes	no	no	no
Ir	2B	yes	no	no	no
Os	2B	yes	no	no	no
Rh	2B	yes	no	no	no
Ru	2B	yes	no	no	no
Se	2B	yes	no	no	no
Ag	2B	yes	no	no	no
Pt	2B	yes	no	no	no
Li	3	yes	no	yes	yes
Sb	3	yes	no	yes	yes
Ba	3	yes	no	no	yes
Mo	3	yes	no	no	yes
Cu	3	yes	no	yes	yes
Sn	3	yes	no	no	yes
Cr	3	yes	no	no	yes

5.5. Evaluation

As the potential elemental impurity identification process is concluded, there are two possible outcomes:

1) The risk assessment process does not identify any potential elemental impurities. The conclusion of the risk assessment and supporting information and data should be documented.

2) The risk assessment process identifies one or more potential elemental impurities. For any elemental impurities identified in the process, the risk assessment should consider if there are multiple sources of the identified elemental impurity or impurities and document the conclusion of the assessment and supporting information.

The applicant's risk assessment can be facilitated with information about the potential elemental impurities provided by suppliers of drug substances, excipients, container closure systems, and manufacturing equipment. The data that support this risk assessment can come from a number of sources that include, but are not limited to:

- Prior knowledge;
- Published literature;
- Data generated from similar processes;
- Supplier information or data;
- Testing of the components of the drug product;
- Testing of the drug product.

During the risk assessment, a number of factors that can influence the level of the potential impurity in the drug product and should also have been considered in the risk assessment. These include but are not limited to:

- Efficiency of removal of elemental impurities during further processing;
- Natural abundance of elements (especially important for the categories of elements which are not intentionally added);
- Prior knowledge of elemental impurity concentration ranges from specific sources;
- The composition of the drug product.

5.6. Summary of risk assessment process

The risk assessment is summarized by reviewing relevant product or component specific data combined with information and knowledge gained across products or processes to identify the significant probable elemental impurities that may be observed in the drug product.

The summary should consider the significance of the observed or predicted level of the elemental impurity relative to the PDE of the elemental impurity. As a measure of the significance of the observed elemental impurity level, a control threshold is defined as a level that is 30% of the established PDE in the drug product. The control threshold may be used to determine if additional controls may be required.

If the total elemental impurity level from all sources in the drug product is expected to be consistently less than 30% of the PDE, then additional controls are not required, provided the applicant has appropriately assessed the data and demonstrated adequate controls on elemental impurities.

If the risk assessment fails to demonstrate that an elemental impurity level is consistently less than the control threshold, controls should be established to ensure that the elemental impurity level does not exceed the PDE in the drug product. (See Section 6)

The variability of the level of an elemental impurity should be factored into the application of the control threshold to drug products. Sources of variability may include:

- Variability of the analytical method;
- Variability of the elemental impurity level in the specific sources;
- Variability of the elemental impurity level in the drug product.

At the time of submission, in the absence of other justification, the level and variability of an elemental impurity can be established by providing the data from three (3) representative production scale lots or six (6) representative pilot scale lots of the component or components or drug product. For some components that have inherent variability (e.g., mined excipients), additional data may be needed to apply the control threshold.

There are many acceptable approaches to summarizing and documenting the risk assessment that may include: tables, written summaries of considerations and conclusions of the assessment. The summary should identify the elemental impurities, their sources, and the controls and acceptance criteria as needed.

5.7. Special considerations for biotechnologically-derived products

For biotechnology-derived products, the risks of elemental impurities being present at levels that raise safety concerns at the drug substance stage are considered low. This is largely because: a) elements are not typically used as catalysts or reagents in the manufacturing of biotech products; b) elements are added at trace levels in media feeds during cell culture processes, without accumulation and with significant dilution/removal during further processing; c) typical purification schemes used in biotech manufacturing such as extraction, chromatography steps and dialysis or Ultrafiltration-Diafiltration (UF/DF) have the capacity to clear elements introduced in cell culture/fermentation steps or from contact with manufacturing equipment to negligible levels. As such, specific controls on elemental impurities up to the biotech drug substance are generally not needed. In cases where the biotechnology-derived drug substance contains synthetic structures (such as antibody-drug conjugates), appropriate controls on the small molecule component for elemental impurities should be evaluated.

However, potential elemental impurity sources included in drug product manufacturing (e.g., excipients) and other environmental sources should be considered for biotechnologically-derived drug products. The contribution of these sources to the finished product should be assessed because they are typically introduced in the drug product manufacture at a step in the process where subsequent elemental impurity removal is not generally performed. Risk factors that should be considered in this assessment should include the type of excipients used, the processing conditions and their susceptibility to contamination by environmental factors (e.g., controlled areas for sterile manufacturing and use of purified water) and overall dosing frequency.

6. Control of elemental impurities

Control of elemental impurities is one part of the overall control strategy for a drug product that assures that elemental impurities do not exceed the PDEs. When the level of an elemental impurity may exceed the control threshold, additional measures should be implemented to assure that the level does not exceed the PDE. Approaches that an applicant can pursue include but are not limited to:

- Modification of the steps in the manufacturing process that result in the reduction of elemental impurities below the control threshold through specific or non-specific purification steps;
- Implementation of in-process or upstream controls, designed to limit the concentration of the elemental impurity below the control threshold in the drug product;
- Establishment of specification limits for excipients or materials (e.g., synthetic intermediates);
- Establishment of specification limits for the drug substance;
- Establishment of specification limits for the drug product;
- Selection of appropriate container closure systems.

Periodic testing may be applied to elemental impurities according to the principles described in ICH Q6A.

The information on the control of elemental impurities that is provided in a regulatory submission includes, but is not limited to, a summary of the risk assessment, appropriate data as necessary, and a description of the controls established to limit elemental impurities.

7. Converting between PDEs and concentration limits

The PDEs, reported in micrograms per day (µg/day) provided in this document give the maximum permitted quantity of each element that may be contained in the maximum daily intake of a drug product. Because the PDE reflects only total exposure from the drug product, it is useful to convert the PDE, into concentrations as a tool in evaluating elemental impurities in drug products or their components. The options listed in this section describe some acceptable approaches to establishing concentrations of elemental impurities in drug products or components that would assure that the drug product does not exceed the PDEs. The applicant may select any of these options as long as the resulting permitted concentrations assure that the drug product does not exceed the PDEs. In the choice of a specific option the applicant must have knowledge of, or make assumptions about, the daily intake of the drug product. The permitted concentration limits may be used:

- As a tool in the risk assessment to compare the observed or predicted levels to the PDE;
- In discussions with suppliers to help establish upstream controls that would assure that the product does not exceed the PDE;
- To establish concentration targets when developing in-process controls on elemental impurities;
- To convey information regarding the controls on elemental impurities in regulatory submissions.

As discussed in Section 5.2, there are multiple sources of elemental impurities in drug products. When applying any of the options described below, elemental impurities from container closure systems and manufacturing equipment should be taken into account before calculating the maximum permitted concentration in the remaining components (excipients and drug substance). If it is determined during the risk assessment that the container closure systems and manufacturing equipment do not contribute to the elemental impurity level in the drug product, they do not need to be considered. Where contributions from container closure systems and manufacturing equipment exist, these contributions may be accounted for by subtracting the estimated daily intake from these sources from the PDE before calculation of the allowed concentration in the excipients and drug substance.

Option 1: Common permitted concentration limits of elements across drug product components for drug products with daily intakes of not more than 10 grams:

This option is not intended to imply that all elements are present at the same concentration, but rather provides a simplified approach to the calculations.

The option assumes the daily intake (amount) of the drug product is 10 grams or less, and that elemental impurities identified in the risk assessment (the target elements) are present in all components of the drug product. Using Equation 1 below, and a daily intake of 10 grams of drug product, this option calculates a common permissible target elemental concentration for each component in the drug. This approach, for each target element, allows determination of a fixed common maximum concentration in micrograms per gram in each component. The permitted concentrations are provided in Appendix 2, Table A.2.2.

$$Concentration(\mu g / g) = \frac{PDE(\mu g / day)}{daily\ \ amount\ of\ drug\ \ product(g / day)} \qquad (1)$$

If all the components in a drug product do not exceed the Option 1 concentrations for all target elements identified in the risk assessment, then all these components may be used in any proportion in the drug product. An example using this option is shown in Appendix 4, Table A.4.2. If the

permitted concentrations in Appendix 2, Table A.2.2 are not applied, Options 2a, 2b, or 3 should be followed.

Option 2a: Common permitted concentration limits across drug product components for a drug product with a specified daily intake:

This option is similar to Option 1, except that the drug daily intake is not assumed to be 10 grams. The common permitted concentration of each element is determined using Equation 1 and the actual maximum daily intake.

This approach, for each target element, allows determination of a fixed common maximum concentration in micrograms per gram in each component based on the actual daily intake provided. An example using this option is provided in Appendix 4, Table A.4.3.

If all components in a drug product do not exceed the Option 2a concentrations for all target elements identified in the risk assessment, then all these components may be used in any proportion in the drug product.

Option 2b: Permitted concentration limits of elements in individual components of a product with a specified daily intake:

This option requires additional information that the applicant may assemble regarding the potential for specific elemental impurities to be present in specific drug product components. The applicant may set permitted concentrations based on the distribution of elements in the components (e.g., higher concentrations in components with the presence of an element in question). For each element identified as potentially present in the components of the drug product, the maximum expected mass of the elemental impurity in the final drug product can be calculated by multiplying the mass of each component material times the permitted concentration established by the applicant in each material and summing over all components in the drug product, as described in Equation 2. The total mass of the elemental impurity in the drug product should comply with the PDEs given in Appendix 2, Table A.2.1. unless justified according to other relevant sections of this guideline. If the risk assessment has determined that a specific element is not a potential impurity in a specific component, there is no need to establish a quantitative result for that element in that component. This approach allows that the maximum permitted concentration of an element in certain components of the drug product may be higher than the Option 1 or Option 2a limit, but this should then be compensated by lower allowable concentrations in the other components of the drug product. Equation 2 may be used to demonstrate that component-specific limits for each element in each component of a drug product assure that the PDE will be met.

$$\mathrm{PDE}(\mu\mathrm{g/day}) \geq \sum_{k=1}^{N} C_k \cdot M_k \qquad (2)$$

k = an index for each of N components in the drug product
C_k = permitted concentration of the elemental impurity in component k (µg/g)
M_k = mass of component k in the maximum daily intake of the drug product (g)

An example using this option is provided in Appendix 4 Tables A.4.4 – A.4.5.

Option 3: Finished Product Analysis:

The concentration of each element may be measured in the final drug product. Equation 1 may be used with the maximum total daily dose of the drug product to calculate a maximum permitted concentration of the elemental impurity. An example using this option is provided in Appendix 4, Table A.4.6.

8. Speciation and other considerations

Speciation is defined as the distribution of elements among chemical species including isotopic composition, electronic or oxidation state, and/or complex or molecular structure. When the toxicities of different species of the same element are known, the PDE has been established using the toxicity information on the species expected to be in the drug product.

When elemental impurity measurements are used in the risk assessment, total elemental impurity levels in drug products may be used to assess compliance with the PDEs. The applicant is not expected to provide speciation information; however, such information could be used to justify lower or higher levels when the identified species is more or less toxic, respectively, than the species used in the monographs in Appendix 3.

When total elemental impurity levels in components are used in the risk assessment, the applicant is not expected to provide information on release of an elemental impurity from the component in which it is found. However, such information could be used to justify levels higher than those based on the total elemental impurity content of the drug product.

9. Analytical procedures

The determination of elemental impurities should be conducted using appropriate procedures suitable for their intended purposes. Unless otherwise justified, the test should be specific for each elemental impurity identified for control during the risk assessment. Pharmacopoeial procedures or suitable alternative procedures for determining levels of elemental impurities should be used.

10. Lifecycle management

The quality systems and management responsibilities described in ICH Q10 are intended to encourage the use of science-based and risk-based approaches at each lifecycle stage, thereby promoting continual improvement across the entire product lifecycle. Product and process knowledge should be managed from development through the commercial life of the product up to and including product discontinuation.

Knowledge gained from development combined with commercial manufacturing experience and data can be used to further improve process understanding and process performance. Such improvements can enhance controls on elemental impurities. It is recognized that the elemental impurity data available for some components is somewhat limited at the date of publication of this guideline, which may direct the applicant to a specific set of controls. Additional data, if developed, may lead to modifications of the controls.

If changes to the drug product or components have the potential to change the elemental impurity content of the drug product, the risk assessment, including established controls for elemental impurities, should be re-evaluated. Such changes could include, but are not limited to: changes in synthetic routes, excipient suppliers, raw materials, processes, equipment, container closure systems or facilities. All changes are subject to internal change management process (ICH Q10) and if needed appropriate regional regulatory requirements.

Glossary

ACGIH:

American Conference of Governmental Industrial Hygienists.

ATSDR:

Agency for Toxic Substances and Disease Registry.

CEC:

Commission of the European Community.

CFR:

Code of Federal Regulations. (USA)

Change Management:

A systematic approach to proposing, evaluating, approving, implementing and reviewing changes. (ICH Q10)

CICAD:

Concise International Chemical Assessment Documents. (WHO)

Container Closure System:

The sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product. A packaging system is equivalent to a container closure system. (ICH Q1A)

Control Strategy:

A planned set of controls, derived from current product and process understanding, that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. (ICH Q10)

Control Threshold:

A limit that is applied during the assessment of elemental impurities to determine if additional control elements may be required to ensure that the PDE is not exceeded in the drug product. The limit is defined as 30% of the PDE of the specific elemental impurity under consideration.

Daily Dose:

The total mass of drug product that is consumed by a patient on a daily basis.

EFSA:

European Food Safety Agency.

EHC:

Environmental Health Criteria. (IPCS, WHO)

EU SCOEL:

European Scientific Committee on Occupational Exposure Limits.

EU SEG:

European Union Scientific Expert Group.

Herbal Products:

Medicinal products containing, exclusively, plant material and/or vegetable drug preparations as active ingredients. In some traditions, materials of inorganic or animal origin can also be present.

IARC:

International Agency for Research on Cancer.

Inhalation Unit Risk:

The upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 µg/L in water, or 1 µg/m^3 in air. The interpretation of inhalation unit risk would be as follows: if unit risk = 2 x 10^{-6} per µg/L, 2 excess cancer cases (upper bound estimate) are expected to develop per 1,000,000 people if exposed daily for a lifetime to 1 µg of the chemical in 1 liter of drinking water. (US EPA)

IPCS:

International Programme for Chemical Safety.

IUPAC:

International Union of Pure and Applied Chemistry.

IRIS:

Integrated Risk Identification System, United States Environmental Protection Agency.

LOAEL:

Lowest-Observed-Adverse-Effect Level: Lowest concentration or amount of a substance *(*dose*)*, found by experiment or observation, that causes an adverse effect on morphology, functional capacity, growth, development, or life span of a target organism distinguishable from normal (control) organisms of the same species and strain under defined conditions of exposure. (IUPAC)

LoQ:

Limit of Quantitation: The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy. The quantitation limit is a parameter of quantitative assays for low levels of compounds in sample matrices, and is used particularly for the determination of impurities and/or degradation products. (ICH Q2)

LOEL:

Lowest-Observed-Effect Level: The lowest dose of substance in a study or group of studies that produces biologically significant increases in frequency or severity of any effects in the exposed humans or animals.

Modifying Factor:

An individual factor determined by professional judgment of a toxicologist and applied to bioassay data to relate that data to human safety. (ICH Q3C) (See related term Safety Factor)

MRL:

Minimal Risk Level: An estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk. (ATSDR)

NAS:

National Academy of Science. (USA)

NOAEL:

No-Observed-Adverse-Effect Level: Greatest concentration or amount of a substance, found by experiment or observation, that causes no detectable adverse alteration of morphology, functional capacity, growth, development, or life span of the target organism under defined conditions of exposure.

NOEL:

No-Observed-Effect Level: The highest dose of substance at which there are no biologically significant increases in frequency or severity of any effects in the exposed humans or animals.

NTP:

National Toxicology Program. (USA)

OEHHA:

Office of Environmental Health Hazard Assessment. (California, USA)

OELV:

Occupational Exposure Limit Value.

OSHA:

Occupational Safety and Health Administration. (USA)

PEL:

Permitted Exposure Limit.

PDE:

Permitted Daily Exposure: The maximum acceptable intake of elemental impurity in pharmaceutical products per day.

Product Lifecycle:

All phases in the life of the product from the initial development through marketing until the product's discontinuation. (ICH Q9)

Quality:

The degree to which a set of inherent properties of a product, system, or process fulfills requirements (see ICH Q6A definition specifically for *quality* of drug substance and drug products). (ICH Q9)

Quality Risk Management:

A systematic process for the assessment, control, communication, and review of risks to the quality of the drug product across the product lifecycle. (ICH Q9)

Quality System:

The sum of all aspects of a system that implements quality policy and ensures that quality objectives are met. (ICH Q10)

Risk:

The combination of the probability of occurrence of harm and the severity of that harm. (ISO/IEC Guide 51, ICH Q9)

Risk Acceptance:

The decision to accept risk. (ISO Guide 73)

Risk Analysis:

The estimation of the risk associated with the identified hazards. (ICH Q9)

Risk Assessment:

A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards. (ICH Q9)

Risk Control:

Actions implementing risk management decisions. (ISO Guide 73)

Risk Identification:

The systematic use of information to identify potential sources of harm (hazards) referring to the risk question or problem description. (ICH Q9)

Risk Management:

The systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating, and reviewing risk. (ICH Q9)

Safety:

Practical certainty that adverse effects will not result from exposure to an agent under defined circumstances. (Ref. 2)

Safety Assessment:

An approach that focuses on the scientific understanding and measurement of chemical hazards as well as chemical exposures, and ultimately the risks associated with them. This term is often (and in this guideline) used synonymously with risk assessment. (Ref. 2)

Safety Factor:

A composite (reductive) factor applied by the risk assessment experts to the NOAEL or other reference point, such as the benchmark dose or benchmark dose lower confidence limit, to derive a reference dose that is considered safe or without appreciable risk, such as an acceptable daily intake or tolerable daily intake (the NOAEL or other reference point is divided by the safety factor to calculate the reference dose). The value of the safety factor depends on the nature of the toxic effect, the size and

type of population to be protected, and the quality of the toxicological information available. See related terms: Assessment factor, Uncertainty factor. (Ref. 2)

Severity:

A measure of the possible consequences of a hazard. (ICH Q9)

TLV:

Threshold Limit Value: The concentration in air to which it is believed that most workers can be exposed daily without an adverse effect (i.e., effectively, the threshold between safe and dangerous concentrations). The values were established (and are revised annually) by the ACGIH and are time-weighted concentrations (TWA) for a 7- or 8-hour workday and 40-hour workweek, and thus related to chronic effects. (IUPAC）

TWA:

Time Weighted Average: As defined by ACGIH, time-weighted average concentration for a conventional 8-hour workday and a 40-hour workweek. (IUPAC)

URF:

Unit Risk Factor.

US DoL:

United States Department of Labor.

US EPA:

United States Environmental Protection Agency.

WHO:

World Health Organization.

References

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3. US EPA. 0410 Boron and Compounds. Integrated Risk Management System (IRIS). 2004.
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Appendix 1: method for establishing exposure limits

For most elements, acceptable exposure levels for elemental impurities in this guideline were established by calculation of PDE values according to the procedures for setting exposure limits in pharmaceuticals (Ref. 1), and the method adopted by International Programme for Chemical Safety (IPCS) for Assessing Human Health Risk of Chemicals (Ref. 2). These methods are similar to those used by the United States Environmental Protection Agency (US EPA) Integrated Risk Information System, the United States Food and Drug Administration (US FDA) (Ref. 3) and others. The method is outlined here to give a better understanding of the origin of the PDE values. When an MRL was used to set the PDE, no additional modifying factors were used as they are incorporated into the derivation of the MRL. For carcinogenic elements unit risk factors were used to set the PDE using a 1:100000 risk level; these are described in the individual monographs in Appendix 3. Some PDEs for inhalation were derived using occupational exposure limits, applying modifying factors, and considering any specific effects to the respiratory system.

The PDE is derived from the No-Observed-Effect Level (NO[A]EL), or the Lowest-Observed-Effect Level (LO[A]EL) in the most relevant animal study as follows:

$$PDE = NO(A)EL \times \text{Mass Adjustment}/[F1 \times F2 \times F3 \times F4 \times F5] \quad (A.1.1)$$

The PDE is derived preferably from a NO(A)EL. If no NO(A)EL is obtained, the LO(A)EL may be used. Modifying factors proposed here, for relating the data to humans, are the same kind of "uncertainty factors" used in Environmental Health Criteria (Ref. 2), and "modifying factors" or "safety factors" in Pharmacopeial Forum.

The modifying factors are as follows:

F1 = A factor to account for extrapolation between species

F1 = 1 for human data

F1 = 5 for extrapolation from rats to humans

F1 = 12 for extrapolation from mice to humans

F1 = 2 for extrapolation from dogs to humans

F1 = 2.5 for extrapolation from rabbits to humans

F1 = 3 for extrapolation from monkeys to humans

F1 = 10 for extrapolation from other animals to humans

F1 takes into account the comparative surface area: body mass ratios for the species concerned and for man. Surface area (S) is calculated as:

$$S = kM^{0.67} \quad (A.1.2)$$

in which M = body mass, and the constant k has been taken to be 10. The body masses used in Equation A.1.2 are those shown below in Table A.1.1.

F2 = A factor of 10 to account for variability between individuals

A factor of 10 is generally given for all elemental impurities, and 10 is used consistently in this guideline

F3 = A variable factor to account for toxicity studies of short-term exposure

F3 = 1 for studies that last at least one half lifetime (1 year for rodents or rabbits; 7 years for cats, dogs and monkeys)

F3 = 1 for reproductive studies in which the whole period of organogenesis is covered

F3 = 2 for a 6-month study in rodents, or a 3.5-year study in non-rodents

F3 = 5 for a 3-month study in rodents, or a 2-year study in non-rodents

F3 = 10 for studies of a shorter duration

In all cases, the higher factor has been used for study durations between the time points, e.g., a factor of 2 for a 9-month rodent study.

F4 = A factor that may be applied in cases of severe toxicity, e.g., non-genotoxic carcinogenicity, neurotoxicity or teratogenicity. In studies of reproductive toxicity, the following factors are used:

F4 = 1 for fetal toxicity associated with maternal toxicity

F4 = 5 for fetal toxicity without maternal toxicity

F4 = 5 for a teratogenic effect with maternal toxicity

F4 = 10 for a teratogenic effect without maternal toxicity

F5 = A variable factor that may be applied if the NOEL was not established

F5 = 1 for a NOEL

F5 = 1-5 for a NOAEL

F5 = 5-10 for a LOEL

F5 = 10 for a Lowest-Observed-Adverse-Effect Level (LOAEL)

For most elements the NOAEL was used to set the oral PDE, using a F5 of 1, as the studies did not investigate the difference between a NOAEL and NOEL and the toxicities were not considered "adverse" at the dose selected for determining the PDE.

The mass adjustment assumes an arbitrary adult human body mass for either sex of 50 kg. This relatively low mass provides an additional safety factor against the standard masses of 60 kg or 70 kg that are often used in this type of calculation. It is recognized that some patients weigh less than 50 kg; these patients are considered to be accommodated by the built-in safety factors used to determine a PDE and that lifetime studies were often used. For lead, the pediatric population is considered the most sensitive population, and data from this population were used to set the PDE. Therefore, the PDEs are considered appropriate for pharmaceuticals intended for pediatric populations.

As an example of the application of Equation A.1.1, consider a toxicity study of cobalt in human volunteers as summarized in Tvermoes (Ref. 4). The NOAEL for polycythemia is 1 mg/day. The PDE for cobalt in this study is calculated as follows:

PDE = 1 mg/day /[1 x 10 x 2 x 1 x 1] = 0.05 mg/day= 50 µg/day

In this example,

F1 = 1 study in humans

F2 = 10 to account for differences between individual humans

F3 = 2 because the duration of the study was 90 days

F4 = 1 because no severe toxicity was encountered

F5 = 1 because a NOAEL was used

Table A.1.1 Values Used in the Calculations in this Document

Rat body weight	425 g	Mouse respiratory volume	43 L/day
Pregnant rat body weight	330 g	Rabbit respiratory volume	1440 L/day
Mouse body weight	28 g	Guinea pig respiratory volume	430 L/day
Pregnant mouse body weight	30 g	Human respiratory volume	28,800 L/day
Guinea pig body weight	500 g	Dog respiratory volume	9,000 L/day
Rhesus monkey body weight	2.5 kg	Monkey respiratory volume	1,150 L/day
Rabbit body weight (pregnant or not)	4 kg	Mouse water consumption	5 mL/day
Beagle dog body weight	11.5 kg	Rat water consumption	30 mL/day
Rat respiratory volume	290 L/day	Rat food consumption	30 g/day

References

1. United States Pharmacopeial Convention, Pharmacopeial Forum, Nov-Dec 1989.
2. IPCS. Assessing Human Health Risks of Chemicals: Derivation of Guidance Values for Health-based Exposure Limits, Environmental Health Criteria 170. International Programme on Chemical Safety. World Health Organization, Geneva. 1994.
3. US FDA, Guidance for Industry and Other Stakeholders: Toxicological Principles for the Safety Assessment of Food Ingredients (Redbook 2000), available at http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm2006826.htm.
4. Tvermoes BE, Unice KM, Paustenbach DJ, Finley BL, Otani JM, Galbraith DA. Effects and blood concentrations of cobalt after ingestion of 1 mg/d by human volunteers for 90 d. Am J Clin Nutr 2014;99:632-46.

Appendix 2: established PDEs for elemental impurities

Table A.2.1 Permitted Daily Exposures for Elemental Impurities1

Element	Class[2]	Oral PDE µg/day	Parenteral PDE, µg/day	Inhalation PDE, µg/day
Cd	1	5	2	2
Pb	1	5	5	5
As	1	15	15	2
Hg	1	30	3	1
Co	2A	50	5	3
V	2A	100	10	1
Ni	2A	200	20	5
Tl	2B	8	8	8
Au	2B	100	100	1
Pd	2B	100	10	1
Ir	2B	100	10	1
Os	2B	100	10	1
Rh	2B	100	10	1
Ru	2B	100	10	1
Se	2B	150	80	130
Ag	2B	150	10	7
Pt	2B	100	10	1
Li	3	550	250	25
Sb	3	1200	90	20
Ba	3	1400	700	300
Mo	3	3000	1500	10
Cu	3	3000	300	30
Sn	3	6000	600	60
Cr	3	11000	1100	3

[1] PDEs reported in this table (µg/day) have been established on the basis of safety data described in the monographs in Appendix 3, and apply to new drug products. The PDEs in the monographs are not rounded. For practical purposes the PDEs in this table have been rounded to 1 or 2 significant figures. PDEs less than 10 have 1 significant figure and are rounded to the nearest unit. PDEs greater than 10 are rounded to 1 or 2 significant figures as appropriate. The principles applied to rounding in this table may be applied to PDEs derived for other routes of administration.

[2] Classification as defined in Section 4.

Table A.2.2 Permitted concentrations of elemental impurities for option 1

The values presented in this table represent permitted concentrations in micrograms per gram for elemental impurities in drug products, drug substances and excipients. These concentration limits are intended to be used when Option 1 is selected to assess the elemental impurity content in drug products with daily doses of not more than 10 grams per day. The numbers in this table are based on Table A.2.1.

Element	Class	Oral Concentration µg/g	Parenteral Concentration µg/g	Inhalation Concentration µg/g
Cd	1	0.5	0.2	0.2
Pb	1	0.5	0.5	0.5
As	1	1.5	1.5	0.2
Hg	1	3	0.3	0.1
Co	2A	5	0.5	0.3
V	2A	10	1	0.1
Ni	2A	20	2	0.5
Tl	2B	0.8	0.8	0.8
Au	2B	10	10	0.1
Pd	2B	10	1	0.1
Ir	2B	10	1	0.1
Os	2B	10	1	0.1
Rh	2B	10	1	0.1
Ru	2B	10	1	0.1
Se	2B	15	8	13
Ag	2B	15	1	0.7
Pt	2B	10	1	0.1
Li	3	55	25	2.5
Sb	3	120	9	2
Ba	3	140	70	30
Mo	3	300	150	1
Cu	3	300	30	3
Sn	3	600	60	6
Cr	3	1100	110	0.3

Appendix 3: individual safety assessments

Antimony

Summary of PDE for Antimony

Antimony (Sb)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	1200	94	22

Introduction

Antimony (Sb) is a silvery white naturally occurring metalloid element that is used in various manufacturing processes. Small amounts of antimony are found in the earth's crust. It exists in of the +3 and +5 oxidation states. Metallic antimony and a few trivalent antimony compounds are the most significant regarding exposure potential and toxicity. Some antimonials, such as Antimony Potassium Tartrate (APT), have been used medicinally as parasiticides. Antimony trioxide is being used as a catalyst (e.g., in the manufacturing of Polyethylene Terephthalate [PET] used for container closure system components). Antimony is nutritionally not essential and no metabolic function is known (ATSDR, 1992). Antimony and antimony trioxide have low solubility in water whereas ATP is water soluble (WHO, 2003).

Safety Limiting Toxicity

APT was negative for mutagenicity in Salmonella in the presence or absence of S9 (NTP, 1992). In a review of genotoxicity data, conflicting results are obtained, although it appears that Sb(3+) may be positive for clastogenicity (WHO, 2003). Available studies are considered inadequate to assess the risk of carcinogenicity by the oral route (Lynch *et al*, 1999). In humans and animals, the gastrointestinal tract appears to be the primary target organ after oral exposure and can result in irritation, diarrhea and vomiting. Antimony is poorly absorbed after oral administration (NTP, 1992). In subchronic studies in rats lower mean body weights and adverse liver findings were the most sensitive endpoints. Inhalation of high levels of antimony over a long period can cause adverse respiratory effects in both humans and animals, including carcinogenicity. In an inhalation carcinogenicity study conducted by Newton *et al.* (1994), rats were exposed to antimony trioxide for 12 months, followed by a 12-month observation period. Neoplasms were observed with comparable incidence among all groups. The authors conclude that Sb_2O_3 was not carcinogenic and propose that in previous studies, positive for carcinogenicity, the tumors may be the result of overload with insoluble particulates (Newton *et al*, 1994; WHO, 2003).

PDE – Oral Exposure

Limited oral data on antimony exposure is available in mice and rats (Schroeder *et al.*, 1968; Schroeder *et al*, 1970; Poon *et al*, 1998). The National Toxicology Program (NTP) conducted a 14-day study in rats and mice where APT was administered in the drinking water. In this study APT was found to be relatively nontoxic by this route (NTP, 1992). Reevaluating the data of Poon *et al.* (1998), Lynch *et al.* concluded that a NOAEL from a 90 day drinking water study in rats using 0.5 to 500 ppm APT was 50 ppm based on lower mean body weight and reduced food consumption at the highest dose (Lynch *et al*, 1999). This finding is consistent with the earlier reports from Schroeder *et al.* (1970). Thus, the PDE for oral exposure was determined on the basis of the lowest NOAEL, i.e., 50 ppm (equivalent to 6.0 mg Sb/kg/day).

Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral PDE is calculated as below:

PDE = 6000 µg/kg/d x 50 kg / 5 x 10 x 5 x 1 x 1 = 1200 µg/day

PDE – Parenteral Exposure

Adverse liver findings (liver capsule inflammation, liver cell necrosis, and liver degeneration.) were the most sensitive endpoint in rats after repeated intraperitoneal administration. Thus, the parenteral PDE was determined on the basis of the lowest NOAEL, i.e., 3.0 mg APT/kg/day (equivalent to 1.1 mg Sb/kg/d). This value was obtained from a 90-day study in rats (based on adverse liver findings at 6 mg/kg in male rats exposed to APT *via* intraperitoneal injection) (NTP, 1992). No systemic effects were observed at this dose.

Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), and correcting for continuous dosing from 3 days per week (factor of 3/7), the parenteral PDE is calculated as below:

PDE = 1100 µg/kg/d x 3/7 x 50 kg / 5 x 10 x 5 x 1 x 1 = 94 µg/day

PDE – Inhalation Exposure

Sub chronic and chronic inhalation rat studies have been conducted. The lung effects observed across these studies were consistent. Using the data from a 13-week inhalation rat study using antimony trioxide dust at exposure levels of 0.25, 1.08, 4.92 and 23.46 mg/m^3, (Newton *et al*, 1994), a NOAEL of 1.08 mg/m^3 was used to determine the inhalation PDE (~83% Sb). At higher dose levels an increase in mean absolute and relative lung weights were observed, a finding not seen in the one year oncogenicity study using exposure levels of 0.06, 0.51 and 4.5 mg/m^3. Carcinogenicity was not observed in this study. No adverse effects on hematology or clinical chemistry were seen in either study.

Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the inhalation PDE is calculated as:

$$\text{For continuous dosing} = \frac{0.9\ \text{mg/m}^3 \times 6\ \text{h/d} \times 5\ \text{d/wk}}{24\ \text{h/d} \times 7\ \text{d/wk}} = \frac{0.16\ \text{mg/m}^3}{1000\ \text{L/m}^3} = 0.00016\ \text{mg/L}$$

$$\text{Daily dose} = \frac{0.00016\ \text{mg/L} \times 290\ \text{L/d}}{0.425\ \text{kg bw}} = 0.11\ \text{mg/kg/day}$$

PDE = 0.11 mg/kg/d x 50 kg / 5 x 10 x 5 x 1 x 1 = 0.022 mg/d = 22 µg/day

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Arsenic

Summary of PDE for Arsenic

Arsenic (As)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	15	15	1.9

Introduction

Arsenic (As) is ubiquitous in the environment and present in food, soil, drinking water and in air. Inorganic arsenic occurs in trivalent (e.g., arsenic trioxide, sodium arsenite) or pentavalent (e.g., sodium arsenate, arsenic pentoxide, arsenic acid) forms. Arsenic has no known useful biological function in human or mammalian organisms. This assessment focuses on inorganic arsenic, because this is most relevant for drug products.

Safety Limiting Toxicity

Inorganic arsenic has shown to be genotoxic, but not mutagenic and has been acknowledged as a human carcinogen (Group 1; IARC, 2012).

Due to its ubiquitous nature and toxicity profile, there have been many risk assessments conducted of arsenic and arsenic compounds, which utilize non-threshold, linear dose response approaches (Meharg and Raab, 2010).

For the most part the effects of arsenic in humans have not been reproduced in animals, so the risk assessments have to rely heavily upon epidemiology data in populations with high exposure concentrations (Schuhmacher-Wolz *et al.*, 2009). In humans, both cancer and non-cancer effects have been linked to arsenic exposure. Oral exposure has been linked to cancers of the skin, liver, lung, kidney and bladder. Following inhalation exposure there is evidence for an increased risk of lung cancer (ATSDR, 2007; IARC, 2012; EU EFSA, 2009; WHO, 2011; US EPA, 2010).

The skin (dyspigmentation, palmoplantar keratosis) and gastrointestinal tract (e.g., nausea) appear to be the most sensitive targets for non-cancer adverse effects after oral ingestion while vascular disease, reproductive effects and neurological effects are also reported as non-cancer endpoints (IARC, 2012; Schuhmacher-Wolz *et al.*, 2009; US EPA, 2007). Oral exposure studies suggest that skin lesions may appear at levels above 0.02 mg As/kg/day; no effects were generally seen at levels from 0.0004 to 0.01 mg As/kg/day (ATSDR, 2007). There are insufficient epidemiological data to set a LOEL or NOEL for other endpoints. The regions of hyperkeratosis may evolve into skin cancers (ATSDR, 2007) and can possibly be considered predictive of skin and internal cancers and the non-cancer long-term adverse health effects (Chen *et al*, 2005; Hsu *et al.*, 2013; Ahsan and Steinmaus, 2013).

Studies of large populations (~40,000) exposed to arsenic concentrations in well water at 1000 µg/L and higher in southwestern Chinese Taipei have been the basis of risk assessments of skin cancer, and more recently of bladder and lung cancer (US EPA, 2010). Recent meta-analyses of cancer risk have indicated no additional bladder cancer risk at low dose exposure (<100–200 µg/L) (Chu and Crawford-Brown, 2006, 2007; Mink *et al.*, 2008). This is consistent with the work of Schuhmacher-Wolz *et al.*, (2009).

An inhalation unit risk for cancer of 0.0043 per µg/m^3 has been established by the US EPA based on data from two US smelters (US EPA, 2007). The Texas Commission on Environmental Quality provided an update to the US EPA Unit Risk Factor (URF), incorporating additional years of follow-up to the US EPA data and additional data on workers from the United Kingdom and Sweden. The Commission

calculated a URF of 0.0015 per μg/m^3. This URF translates to an air concentration of 0.067 μg/m^3 at a risk of 1 in 100,000 excess lung cancer mortality (Erraguntla *et al.*, 2012).

PDE – Oral Exposure

The oral PDE is based on the chronic effects of arsenic to skin and sets the limit at 15 μg/day based on Agency for Toxic Substances and Disease Registry (ATSDR) MRL and US EPA limit of 0.0003 mg/kg/day (ATSDR, 2007; US EPA 2007; EU EFSA, 2009). The PDE calculated based on the ATSDR MRL is consistent with drinking water standards (WHO, 2011).

PDE = 0.0003 mg/kg/d x 50 kg = 0.015 mg/d = 15 μg/day

No modifying factors were applied because they are incorporated into the derivation of the MRL.

PDE – Parenteral Exposure

The oral bioavailability of arsenic is ~95%. The most direct evidence is from a study that evaluated the 6-day elimination of arsenic in healthy humans who were given water from a high-arsenic sampling site (arsenic species not specified) and that reported approximately 95% absorption (Zheng *et al.*, 2002). Therefore the PDE is identical to the oral PDE.

PDE = 15 μg/day

PDE – Inhalation Exposure

Increased risk of lung cancer and other respiratory disorders have been reported following inhalation exposure to workers in the occupational setting. The rationale for using a cancer endpoint for inhalation to set the PDE is the relative lack of information on linear-dose extrapolation, as compared to the oral route. No modifying factors are needed as the URF were determined for the protection of the general public. Based on the assessment conducted by Erraguntla *et al.* (2012), based on the risk of 1:100.000, the inhalation PDE is:

PDE = 0.067 μg/m^3 / 1000 L/m^3 x 28800 L/d = 1.9 μg/day

No modifying factors were applied because the PDE is based on a URF derived from the multiplicate relative risk model described by Erraguntla *et al.* (2012).

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Barium

Summary of PDE for Barium

Barium (Ba)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	1460	730	343

Introduction

Barium (Ba) is a dense, silver-white, soft alkaline earth metal that oxidizes readily in moist air and reacts with water. The Ba(2+) ion and the water soluble compounds of barium (chloride, nitrate, hydroxide) are toxic. The insoluble compounds of barium, such as barium sulfate, do not generate free Ba(2+) ions in the gastrointestinal tract and therefore are generally nontoxic to humans. Barium is nutritionally not essential and no metabolic function is known. Barium sulfate has multiple uses e.g., as a radiocontrast medium, a colorant in paint and in the manufacture of glass and other products (ATSDR, 2007).

Safety Limiting Toxicity

In animals and humans, the kidney appears to be the most sensitive target of toxicity resulting from repeated ingestion of soluble barium salts. Chronic rodent studies support the evidence for an association between barium exposure and renal toxicity (NTP, 1994). The lesions were characterized by tubule dilatation, renal tubule atrophy, tubule cell regeneration, hyaline cast formation, multifocal interstitial fibrosis, and the presence of crystals, primarily in the lumen of the renal tubules. These changes were characterized as morphologically distinct from the spontaneous degenerative renal lesions commonly observed in aging mice. Effects on blood pressure may be the most sensitive endpoint observed in humans after environmental exposure (WHO, 2004). Repeated exposure to barium oxide *via* inhalation may cause bronchitis, including cough, phlegm, and/or shortness of breath (CICAD, 2001).

PDE – Oral Exposure

In an evaluation conducted in two towns in Illinois, no significant differences in blood pressure or in the prevalence of cardiovascular or kidney disease was found between populations drinking water containing a mean barium concentration of 7.3 mg/L or 0.1 mg/L (WHO, 2004). Using the NOAEL of 7.3 mg/L obtained from this study, and using 2 L/day as an estimation of water intake, the oral PDE can be calculated as:

PDE = 14.6 mg/d / 1 x 10 x 1 x 1 x 1 = 1.46 mg/d =1460 µg/day

PDE – Parenteral Exposure

No relevant data on parenteral exposure to barium compounds were found. The bioavailability of barium is estimated to be 20-60% in adults and infants, respectively (ATSDR, 2007). Thus, the parenteral PDE was calculated by dividing the oral PDE by a modifying factor of 2 (as described in Section 3.1).

PDE = 1460 µg/d / 2 = 730 µg/day

PDE – Inhalation Exposure

No relevant data on inhalation exposure to barium compounds were found. United States Department of Labor (US DoL, 2013) has a reported Time Weighted Average (TWA) of 0.5 mg/m^3 based on soluble barium salts.

Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the inhalation PDE is calculated as:

$$\text{For continuous dosing} = \frac{500\ \mu g/\ m^3 \times 8\ hr/d \times 5\ d/wk}{24\ hr/d \times 7\ d/wk} = \frac{119\ \mu g/\ m^3}{1000\ L/m^3} = 0.119\ \mu g/L$$

$$\text{Daily dose} = \frac{0.119\ \mu g/L \times 28800\ L}{50\ kg} = 68.6\ \mu g/kg$$

PDE = 68.6 µg/kg x 50 kg / 1 x 10 x 1 x 1 x 1 = 343 µg/day

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Cadmium

Summary of PDE for Cadmium

Cadmium (Cd)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	5.0	1.7	1.7

Introduction

Cadmium (Cd) is a transition metal whose most abundant naturally-occurring isotope is non-radioactive. It is found in nature in mineral forms and is obtained for commercial uses principally from cadmium ore (ATSDR, 2012). Cadmium exists as a salt form in the +2 oxidation state only. Some cadmium salts such as cadmium chloride, cadmium sulfate and cadmium nitrate are water soluble; other insoluble salts can become more soluble by interaction with acids, light or oxygen. Cadmium, cadmium oxide, cadmium salts on borosilicate carrier are used as catalysts in organic synthesis. Silver cadmium alloy is used in the selective hydrogenation of carbonyl compounds.

Safety Limiting Toxicity

Cadmium has shown to be genotoxic, but not mutagenic and has been acknowledged as a human carcinogen (Group 1; IARC, 2012). Cadmium and cadmium compounds cause cancer of the lung. Also, positive associations have been observed between exposure to cadmium and cadmium compounds and cancer of the kidney and of the prostate.

A sensitive endpoint for oral exposure to cadmium and cadmium salts is renal toxicity (Buchet *et al*. 1990). Skeletal and renal effects are observed at similar exposure levels and are a sensitive marker of cadmium exposure (ATSDR, 2012).

Evidence from numerous epidemiologic studies assessing inhalation exposures to cadmium *via* both occupational and environmental routes has demonstrated an increased risk of developing cancer (primarily lung) that correlates with inhalation exposure to cadmium (IARC, 2012; NTP, 1995). An inhalation unit risk of 0.0018/µg/m^3 has been derived by the US EPA (1992).

PDE – Oral Exposure

A sensitive endpoint for oral exposure to cadmium and cadmium salts is renal toxicity (Buchet *et al*, 1990). Skeletal and renal effects are observed at similar exposure levels and are a sensitive marker of cadmium exposure (ATSDR, 2012). A number of oral exposure studies of cadmium in rats and mice showed no evidence of carcinogenicity. Therefore the renal toxicity endpoint was used to establish the oral PDE for cadmium, following the recommendations of ATSDR, an MRL of 0.1 µg/kg for chronic exposure is used to set the oral PDE. This is consistent with the WHO drinking water limit of 0.003 mg/L/day (WHO, 2011).

PDE = 0.1 µg/kg/d x 50 kg = 5.0 µg/day

No modifying factors were applied because they are incorporated into the derivation of the MRL.

PDE – Parenteral Exposure

A 12-week study in rats given daily subcutaneous injections of 0.6 mg/kg Cd, 5 days per week showed renal damage at week 7 and later (Prozialeck *et al*, 2009). A single dose level was used in this study. The LOAEL of this study is 0.6 mg/kg based on decreased body weight, increased urine volume and urinary biomarkers seen at this dose level. This study was used to set the parenteral PDE. In a separate single dose study where rats were administered a 0, 1, 2, 4, 8, 16 or 32 µmol/kg cadmium chloride by the subcutaneous route, sarcomas were noted at the injection site at the two highest doses

at the end of the 72 week observation period (Waalkes *et al*, 1999). It is uncertain whether the granulomas at the sites of injection over time trap an unspecified amount of the administered cadmium dose at the injection site. This phenomenon may decrease the actual parenteral cadmium dose, compared with the calculated parenteral cadmium dose. Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), and correcting for continuous dosing from 5 days to 7 days per week (factor of 5/7), the parenteral PDE is calculated as:

PDE = 0.6 mg/kg x 5/7 x 50 kg / 5 x 10 x 5 x 5 x 10 = 1.7 µg/day

A factor of 5 was chosen for F4 because cadmium is carcinogenic by the inhalation route and granulomas were observed by the subcutaneous route. These findings are of uncertain relevance. A factor of 10 was chosen for F5 because a LOAEL was used to set the PDE.

PDE – Inhalation Exposure

Using the inhalation unit risk of 0.0018/µg/m^3 that has been derived for cadmium and a risk level of 1:100000, the inhalation PDE can be calculated as:

$$\text{Inhalation PDE} = \frac{1\text{x}10^{-5}}{1.8\ \text{x}10^{-3}\ /\mu\text{g/m}^3} = 5.55 \text{ x } 10^{-2}\ \mu\text{g/m}^3$$

PDE = 0.056 µg/m^3 / 1000 L/m^3 x 28800 L/d = 1.7 µg/day

No modifying factors are used to adjust a PDE derived by the unit risk approach.

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Chromium

Summary of PDE for Chromium

Chromium (Cr)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	10700	1070	2.9

Introduction

Chromium (Cr) is found in a variety of oxidation states, the most important being Cr(0) (in stainless steel) Cr(2+), Cr(3+) and Cr(6+). Cr (2+) is readily oxidized and is used as a reducing agent in chemical synthesis. Cr(6+) is a powerful oxidant, chromate, CrO_4^{2-}, and dichromate, $Cr_2O_7^{2-}$, being the best known oxyanions. Cr(3+), the most abundant environmental form, is an essential element that plays a role in glucose metabolism. Chromium deficiency causes changes in the metabolism of glucose and lipids and may be associated with maturity-onset diabetes, cardiovascular diseases, and nervous system disorders (Anderson, 1993, 1995). Sources of chromium in pharmaceuticals may include colorants, leaching from equipment or container closure systems, and catalysts. Except when it is used as a catalyst, intake of chromium from pharmaceuticals will be in the form of metallic chromium (Cr(0)) or Cr(3+) rather than the more toxic Cr(6+); therefore, for drug products, this safety assessment is based on the known toxicity of Cr(3+) and Cr(6+) is excluded from this assessment. If Cr(6+) is used as a catalyst, then the assessment should incorporate this form. Chromium present as a colorant (e.g., chromium oxide green, chromium hydroxide green) is intentionally added and thus beyond the scope of this guidance.

Safety Limiting Toxicity

Rats fed diets containing up to 5% Cr_2O_3 (equivalent to 1468 mg Cr/kg/day) for a lifetime showed no adverse effects. In a more recent dietary rat study (Anderson *et al*, 1997), no adverse effects were detected at 15 mg Cr(3+)/kg/day. No specific target organ toxicities have been identified for the oral intake of chromium. Generally oral intake of 1.5 mg/kg/day Cr(3+) (US EPA, 1998) is not expected to be associated with adverse health.

The data was reviewed to identify the safety limiting toxicities based on routes of administration.

PDE – Oral Exposure

The 2-year NTP studies (2010) on the carcinogenicity of Cr(3+) picolinate administered in feed to rats and mice at 2000, 10000 and 50000 ppm provided the most relevant safety information for chromium as present in drug products. The NOAEL was the low dose of 90 mg/kg Cr(3+) picolinate (11.9 weight %; 10.7 mg/kg/day Cr(3+)) in rats based on increase in the incidence of preputial gland adenoma in male rats at 460 mg/kg. This finding was not dose-dependent and was considered an equivocal finding by the study authors. This finding was not observed male mice or in the female counterpart in either species (clitoral gland). Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral PDE is calculated as:

PDE = 10.7 mg/kg/d x 50 kg / 5 x 10 x 1 x 1 x 1 = 10.7 mg/day

PDE – Parenteral Exposure

Recommendation for the nutritional intravenous administration of Cr(3+) vary per age group between 0.05 µg/kg/day in preterm infants and 15 µg/kg in adults (Moukazel, 2009). There is insufficient information to assess if exceeding these recommended daily doses may lead to adverse responses e.g., for the kidney especially in newborns and preterm infants.

The safety review for chromium was unable to identify any significant assessments upon which to calculate a PDE for parenteral routes of exposure. On the basis of an oral bioavailability of about 10% for chromium and inorganic chromium compounds (ATSDR, 2012), the parenteral PDE was calculated by dividing the oral PDE by a modifying factor of 10 (as described in Section 3.1). The recommended PDE for chromium for parenteral exposure is:

PDE = 10700 µg/d / 10 = 1070 µg/day

PDE – Inhalation Exposure

The study by Derelenko *et al.* (1999) used inhalation of Cr(3+) sulfate particles during 13 weeks (6h/day and 5 days per week), and the predominant observed effects were chronic inflammation of the airways (mononuclear infiltrate, particular material) and local thickening of alveolar walls. The effect was observed at all doses. The LOAEL is 17 mg/m^3 (3 mg Cr(3+)/m^3). A lack of systemic toxicity was noted in a 13-week inhalation study in rats administered soluble or insoluble Cr(3+). Based on these data, the inhalation MRL of 0.1µg/m^3 was used to set the PDE (ATSDR, 2012).

PDE =0.0001 mg/m^3 / 1000 m^3/L x 28800 L/day = 2.9 µg/day

No modifying factors were applied because they are incorporated into the derivation of the MRL.

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Cobalt

Summary of PDE for Cobalt

Cobalt (Co)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	50	5.0	2.9

Introduction

Cobalt (Co) is a naturally-occurring element, often combined with other elements such as oxygen, sulfur, and arsenic. Cobalt is essential in the human body because it is an integral component of Vitamin B12 and functions as a co-enzyme for several enzymes critical in the synthesis of hemoglobin and the prevention of pernicious anemia. The average person receives about 11 µg Co/day in the diet (ATSDR, 2004). The Recommended Dietary Allowance of Vitamin B12 ranges from 0.7 to 2.4 µg/day (NAS, 2010), which corresponds to 0.03 to 0.1 µg of cobalt. No essential biological function of inorganic cobalt in the human body has been identified. Cobalt compounds (e.g., cobalt octanoate) are being used as catalysts in selective hydrogenation.

Safety Limiting Toxicity

The International Agency for Research on Cancer (IARC, 2006) concluded that Cobalt sulfate and other soluble Co(2+) salts are possible human carcinogens (Group 2B). The data indicate the location of tumors is limited to the lung in rats and humans. Cobalt metal was positive for mutagenicity *in vitro* but negative for clastogenicity *in vivo*. The NTP concluded that there was clear evidence of carcinogenicity in male and female mice and rats (NTP, 2013). Human studies for carcinogenicity by inhalation are inconclusive and not classified for carcinogenicity (US EPA, 2000). Polycythemia is considered to be the most sensitive finding after repeated oral exposure to humans (ATSDR, 2004). Inhalation exposure of humans to cobalt has been associated with a severe and progressive respiratory disease known as hard-metal pneumoconiosis, as well as asthma and contact dermatitis (ATSDR, 2004; IARC, 2006).

PDE – Oral Exposure

The oral PDE is based on the available human data. Polycythemia was a sensitive endpoint in humans after repeated oral exposure to 150 mg of cobalt chloride for 22 days (~1 mg Co/kg/day; WHO, 2006; ATSDR, 2004). Polycythemia or other effects were not observed in a study of 10 human volunteers (5 men and 5 women) ingesting 1 mg/Co per day as $CoCl_2$ for 88-90 days (Tvermoes *et al*, 2014). The oral PDE was determined on the basis of the NOAEL of 1 mg/day. Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral PDE is calculated as below:

PDE = 1 mg/d / 1 x 10 x 2 x 1 x 1 = 0.05 mg/d = 50 µg/day

A factor of 2 was chosen for F3 because a short term human study was used to set the PDE.

PDE – Parenteral Exposure

No relevant data on parenteral exposure to cobalt compounds were found. The oral bioavailability of cobalt and inorganic cobalt compounds ranges from 18-97% (ATSDR, 2004). To account for the low oral bioavailability, the parenteral PDE was calculated by dividing the oral PDE by a modifying factor of 10 (as described in Section 3.1). The PDE for cobalt for parenteral exposure is:

PDE = 50 µg/d / 10 = 5.0 µg/day

PDE – Inhalation Exposure

Cobalt sulfate and other soluble Co(2+) salts are possible human carcinogens (Group 2B) that can induce lung tumors.

Pneumoconiosis, asthma and contact dermatitis were the principal non-carcinogenic effects in humans after chronic inhalation. The MRL approach was considered acceptable for cobalt as the data are considered more reliable and the lack of human data for carcinogenicity cobalt sulfate. The best estimate of human cancer risk is approximately the same as the PDE derived using the MRL (WHO, 2006). For the calculation of the inhalation PDE, the chronic inhalation MRL of 0.1 µg/ m^3 was used (ATSDR, 2004).

PDE = 0.0001 mg/ m^3 /1000 m^3/L x 28800 L/d = 2.9 µg/day

No modifying factors were applied because they are incorporated into the derivation of the MRL.

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Copper

Summary of PDE for Copper

Copper (Cu)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	3400	340	34

Introduction

Copper (Cu) is a Group 11 element of the first transition series and has two main oxidation states, Cu(1+) and Cu(2+). It is an essential trace element in both animals and humans. Copper plays a vital role in a number of critical enzyme systems and is closely linked with normal hematopoiesis and cellular metabolism. Copper compounds (e.g., copper chromite) are being used as catalysts in hydrogenolysis and decarboxylation reactions.

Safety Limiting Toxicity

A general review of relevant safety data for animals and humans indicates that copper can produce adverse effects to the gastrointestinal tract, liver, and kidney upon ingestion of toxic doses (Araya *et al*, 2003).

PDE – Oral Exposure

Studies on cupric sulfate and copper 8-quinolinolate have been conducted in mice, rats and dogs (IPCS, 1998). Rats were determined to be the most sensitive of these species to effects on liver and kidney. In a 13-week study in which rats were fed 500 to 8000 ppm cupric sulfate pentahydrate, the NOEL for hyperplasia and hyperkeratosis of the forestomach mucosa was 1000 ppm. Hepatic and renal toxicity was observed from doses equal to and greater than 2000 ppm. The NOEL was 1000 ppm, equivalent to 64 mg $CuSO_4$/kg/day (17 mg Cu/kg/day). (Hébert *et al*, 1993; IPCS, 1998). Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral PDE is calculated as:

PDE = 17 mg/kg/d x 50 kg / 5 x 10 x 5 x 1 x 1 = 3400 µg/day

PDE – Parenteral Exposure

The safety review for copper was unable to identify any significant assessments upon which to calculate a PDE for parenteral routes of exposure. The human gastrointestinal system can absorb 30-40% of ingested copper from the typical diets consumed in industrialised countries (Wapnir, 1998). On the basis of limited oral bioavailability of 30-40% for copper and inorganic copper salts, the parenteral PDE was calculated by dividing the oral PDE by a modifying factor of 10 (as described in Section 3.1). The recommended PDE for copper for parenteral exposure is:

PDE = 3400 µg/d / 10 = 340 µg/day

PDE – Inhalation Exposure

The available data on the toxicity of inhaled copper were considered inadequate for derivation of acute-, intermediate-, or chronic-duration inhalation MRLs (ATSDR, 2004). The inhalation PDE was calculated by dividing the oral PDE by a modifying factor of 100 (as described in Section 3.1).

PDE = 3400 µg/day / 100 = 34 µg/day

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Gold

Summary of PDE for Gold

Gold (Au)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	134	134	1.3

Introduction

Gold (Au) exists in metallic form and in oxidation states of +1 to +5, the monovalent and trivalent forms being the most common. Elemental gold is poorly absorbed and consequently is not considered biologically active. Gold is being used on a carrier or in complexes like gold chloride and L-Au^+ (where L is a phosphane, phosphite, or an arsine; Telles, 1998), as catalysts in organic synthesis. The only source for gold in drug products comes from the use as catalyst. Au(1+) salts are used therapeutically.

Safety Limiting Toxicity

Most knowledge of gold toxicity is based on therapeutic uses of gold. Currently available therapies are gold salts of monovalent Au(1+) with a sulfur ligand (Au-S), but metallic gold has also been studied. No toxicity was seen in 10 patients administered colloidal metallic gold (monoatomic gold) at 30 mg/day for one week followed by 60 mg/day the second week or the reverse schedule. The patients were continued on the trial for an additional 2 years at 30 mg/day. There was no evidence of hematologic, renal or hepatic cytotoxicity but some improvement in clinical symptoms of rheumatoid arthritis and in cytokine parameters were noted (Abraham and Himmel, 1997).

Long term animal and human data are available with gold compounds. Toxicities include renal lesions in rats administered gold compounds by injection (Payne and Saunders, 1978) and humans (Lee *et al*, 1965) and gastrointestinal toxicity in dogs (Payne and Arena, 1978). However, these studies have been performed with monovalent gold (Au(1+)) or forms of gold not present as pharmaceutical impurities and thus are not considered sufficiently relevant to derive a PDE for gold in pharmaceutical products.

There are no relevant toxicology studies in humans or animals by the oral route of a form of gold likely to be in a pharmaceutical product to set an oral PDE of gold. Au(3+) is thought to be the more toxic form and is used in catalysis, e.g., as gold trichloride. There is only limited data on Au(3+) complexes. In one study, the Au(3+) compound $[Au(en)Cl_2]Cl$ (dichloro(ethylenediamine-aurate^{3+} ion) caused minimal histological changes in the kidney and liver of rats, and no renal tubular necrosis, at a dose of 32.2 mg/kg in mice administered the compound intra peritoneal for 14 days (Ahmed *et al*, 2012).

PDE – Oral Exposure

The toxicologically significant endpoint for gold exposures is renal toxicity. The study in mice administered Au(3+) by the intra peritoneal route was considered acceptable in setting the oral PDE because the renal endpoint of toxicity is a sensitive endpoint of gold toxicity. Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral PDE is calculated as:

PDE = 32.2 mg/kg x 50 kg / 12 x 10 x 10 x 1 x 10 = 134 µg/day

A factor of 10 for F5 was chosen because the LOAEL is used to establish the PDE and the toxicological assessment was not complete.

PDE – Parenteral Exposure

In humans, 50 mg intramuscular injections of gold sodium thiomalate resulted in >95% bioavailability (Blocka *et al*, 1986). In rabbits, approximately 70% of the gold sodium thiomalate was absorbed after an intramuscular injection of 2/mg/kg (Melethil and Schoepp, 1987). Based on high bioavailability, and that a study by the intra peritoneal route was used to set the oral PDE, the parenteral PDE is equal to the oral PDE.

PDE = 134 µg/day

PDE – Inhalation Exposure

In the absence of relevant inhalation and parenteral data, including the potential local tissue toxicity of the effects of gold in lungs, the parenteral PDE was calculated by dividing the oral PDE by a modifying factor of 100 (as described in Section 3.1).

PDE = 134 µg/d / 100 = 1.34 µg/day

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Lead

Summary of PDE for Lead

Lead (Pb)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	5.0	5.0	5.0

Introduction

Lead (Pb) occurs in organic and inorganic forms. The generally bivalent lead compounds include water-soluble salts such as lead acetate as well as insoluble salts such as lead oxides. Organic lead compounds include the gasoline additives tetramethyl- and tetraethyl-lead. Organic lead compounds undergo fairly rapid degradation in the atmosphere and form persistent inorganic lead compounds in water and soil. Lead has no known biological function in human or mammalian organisms (ATSDR, 2007).

Safety Limiting Toxicity

In humans and animals, exposure to lead may cause neurological, reproductive, developmental, immune, cardiovascular and renal health effects. In general, sensitivity to lead toxicity is greater when there is exposure in utero and in children compared to adults. A target blood level of 1-2 µg/dL was set, and using modelling programs (US EPA, 2009) that assumed 100% bioavailability and no other exposure, a PDE was obtained. For this reason, the PDEs are the same regardless of the route of administration.

PDE – Oral Exposure

Adverse neurobehavioral effects are considered to be the most sensitive and most relevant endpoint in humans after oral exposure. Data from epidemiological studies show that blood lead levels <5 µg/dL may be associated with neurobehavioral deficits in children (NTP, 2011).

According to the US EPA model (Integrated Exposure Uptake Biokinetic (IEUBK) Model, 1994) (100% absorption, no other sources of lead), oral intake of 5 µg/day translates into a blood level of 1-2 µg/dL for children age 0-7 years (0-82 months) (US EPA, 2007, 2009).

PDE = 5.0 µg/day

PDE – Parenteral Exposure

The oral effects of Pb are based on blood levels. Therefore, the parenteral PDE is equal to the oral PDE.

PDE = 5.0 µg/day

PDE – Inhalation Exposure

The oral effects of Pb are based on blood levels. Therefore, the inhalation PDE is equal to the oral PDE.

PDE = 5.0 µg/day

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Lithium

Summary of PDE for Lithium

Lithium (Li)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	560	280	25

Introduction

Lithium (Li) is a common metal that is present in plant and animal tissues. Lithium is being used alone or in combination with other metals as catalyst. Lithium compounds (e.g., lithium aluminum hydride) are being used as reagents in organic synthesis. Lithium exists commonly as a salt in the +1 oxidation state only.

Safety Limiting Toxicity

Lithium is used as a human therapeutic, and extensive human data exists in the administration of lithium salts in the treatment of mania, bipolar disorder, and recurrent unipolar depression. Treatment with lithium salts requires frequent controls by the treating physician, including measurement of lithium concentrations. The therapeutic range for lithium has been established at 0.6-1 mmol/L in serum, depending upon the formulation administered (Grandjean and Aubry, 2009). The therapeutic margin is narrow and Li toxicity can occur at therapeutic exposures. Lithium treatment in humans is mainly associated with an increased risk of reduced urinary concentrating ability, hypothyroidism, hyperparathyroidism, and weight gain (McKnight *et al*, 2012). The usual recommended dose is 300-600 mg three to four times a day (US FDA, 2011). The data was reviewed to identify the safety limiting toxicities based on routes of administration.

PDE – Oral Exposure

Human experience with lithium was used as the point of departure for this PDE. When using the lowest human single oral dose of 300 mg lithium carbonate (56 mg Li), the oral PDE is calculated as follows:

PDE = 56 mg/d / 1 x 10 x 1 x 1 x 10 = 0.56 mg/d = 560 µg/day

A factor of 10 was chosen for F5 because a LOAEL (one-third the recommended daily dose) was used to set the PDE.

PDE – Parenteral Exposure

There are no adequate data to develop a parenteral PDE. However, based on oral bioavailability of 85% (Grandjean and Aubry, 2009), the parenteral PDE was calculated by dividing the oral PDE by a modifying factor of 2 (as described in Section 3.1).

PDE = 560 µg/d / 2 = 280 µ/day

PDE – Inhalation Exposure

Rabbits were exposed to lithium chloride at 0.6 and1.9 mg/m^3 for 4-8 weeks, 5 days/week for 6 hours/d (Johansson *et al.* 1988). Lungs were studied by light and electron microscopy with focus on inflammatory changes. No significant effects were reported, so the highest dose was used to set the PDE. Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the inhalation PDE is calculated as:

$$\text{For continuous dosing} = \frac{1.9\ \text{mg/m}^3 \times 6\ \text{h/d} \times 5\ \text{d/wk}}{24\ \text{h/d} \times 7\text{d/wk}} = \frac{0.34\ \text{mg/m}^3}{1000\ \text{L/m}^3} = 0.00034\ \text{mg/L}$$

$$\text{Daily dose} = \frac{0.00034\ \text{mg/L} \times 1440\ \text{L/d}}{4\ \text{kg}} = 122.04\ \mu\text{g/kg/day}$$

PDE = 122.04 µg/kg/d x 50 kg / 2.5 x 10 x 10 x 1 x 1 = 25 µg/day

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Mercury

Summary of PDE for Mercury

Mercury (Hg)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	30	3.0	1.2

Introduction

Mercury (Hg) is widely distributed in the global environment. Mercury exists in three forms: elemental mercury, inorganic mercury and organic mercury. The most likely form of residual mercury in drug products is the inorganic form. Therefore, this safety assessment is based on the relevant toxicological data of elemental or inorganic mercury. This safety assessment and derived PDEs do not apply to organic mercury.

Safety Limiting Toxicity

There is no data to indicate that inorganic mercury is carcinogenic in human. There is limited evidence in experimental animals for the carcinogenicity of mercuric chloride. The International Agency for Research on Cancer (IARC) concluded that inorganic mercury compounds are not classifiable as to their carcinogenicity to humans (Group 3; IARC, 1997).

Inorganic mercury compounds show significantly lower oral bioavailability compared to organic mercury and induce different toxicological effects including neurological, corrosive, hematopoietic, and renal effects and cutaneous disease (acrodynia). The safety limiting toxicity for inorganic mercury and salts is renal toxicity. Direct absorption to the brain *via* the olfactory pathway has been reported (Shimada *et al*, 2005).

PDE – Oral Exposure

There were well designed NTP studies in rats and mice of $HgCl_2$ of up to 2 years duration. The 6-month gavage study in rats was selected because it had more detailed clinical pathology assessment and a wider range of doses (0.312 to 5 mg $HgCl_2$/kg/5d per week) than the 2-year study. Absolute and relative (to body weight) kidney weights were increased from 0.625 mg/kg. Some changes in clinical chemistry parameters (decreased creatinine, potassium, alanine aminotransferase and aspartate aminotransferase) were noted in all dosed males. The findings did not appear dose-dependent. An increase in the incidence and severity (minimal to mild) in nephropathy was noted from 0.625 mg $HgCl_2$. In a Joint Expert Committee for Food Additives (JECFA) assessment (JECFA, 2011) a $BMDL_{10}$ of 0.06 mg Hg/kg/day (adjusted from 5 days/week dosing) was derived based on adverse renal effects (weight increase) from the 6-month rat study (NTP, 1993). Using the modifying factors (F1-F5 as discussed in Appendix 1) the oral PDE is calculated as:

PDE = 0.06 mg/kg/d x 50 kg / 5 x 10 x 2 x 1 x 1 = 0.03 mg/d = 30 µg/day

F4 was set to 1 as the findings in the 6-month and 2-year studies were not considered significant at the lowest dose, and F5 was set to 1 as the $BMDL_{10}$ can be considered a NOAEL (Sargent *et al*, 2013).

PDE – Parenteral Exposure

Animal studies indicate that the oral bioavailability of inorganic mercury is in the 10-30% range (ATSDR, 1999). Therefore, the parenteral PDE was calculated by dividing the oral PDE by a modifying factor of 10 (as described in Section 3.1).

PDE = 30 µg/d / 10 = 3.0 µg/day

PDE – Inhalation Exposure

Neurobehavioral effects are considered to be the most sensitive endpoint following inhalation exposure in humans as shown in occupational studies at the range of air TWA levels between 14 and 20 µg/m^3 (US EPA, 1995; EU SCOEL, 2007). The presence of neurobehavioral effects at low-level mercury exposures (14 µg/m^3) in dentists (Ngim *et al.* 1992) indicates that the TWA needs to be considered as a LOAEL. Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the inhalation PDE is calculated based on the long-term inhalation exposure to elemental mercury vapor:

$$\text{For continuous dosing} = \frac{14\ \mu g/m^3 \times 8\ hr/d \times 6\ d/wk}{24\ hr/d \times 7\ d/wk} = \frac{4\ \mu g/m^3}{1000\ L/m^3} = 0.004\ \mu g/L$$

$$\text{Daily dose} = \frac{0.004\ \mu g/L \times 28800\ L}{50\ kg} = 2.30\ \mu g/kg$$

PDE = 2.30 µg/kg x 50 kg / 1 x 10 x 1 x 1 x 10 = 1.2 µg/day

A factor of 10 for F5 was chosen because a LOAEL was used to set the PDE and to account for the possible direct transfer of mercury to the brain through the olfactory pathway.

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Molybdenum

Summary of PDE for Molybdenum

Molybdenum (Mo)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	3400	1700	11

Introduction

The main oxidation states for Mo are +4 and +6, the most common forms of which are oxyanions. The predominant form of Mo occurring in soils and natural waters is the molybdate ion, MoO_4^{2-} which forms soluble compounds with a variety of cations including K^+, NH_4^+ and Ca^{2+}. Mo exists in soil in various forms at concentration of 0.1-10 mg/kg. MoO_2 and MoS_2 are insoluble in water. It is widely present in vegetables, dairy products and meats. Mo combinations (e.g., Bi-Mo, Fe-Mo, molybdenum oxide and Mo-complexes) are being used as catalysts in organic synthesis.

Molybdenum is an essential element with an estimated upper level intake range of 100-600 µg/day for infants to adults, respectively (EC Scientific Committee on Food, 2000). Molybdenum deficiency is characterized by night blindness, nausea, disorientation, coma, tachycardia and tachypnea and associated with various biochemical abnormalities including high plasma methionine. In addition an almost undetectable serum uric acid concentration has been reported in a patient receiving total parenteral nutrition (Abumrad *et al*, 1981).

Safety Limiting Toxicity

Molybdenum as the trioxide was not mutagenic (NTP, 1997) and a Ruksinstutuut Voor Volksgezondheid En Milieu (RIVM) assessment concluded that molybdenum is not genotoxic (RIVM, 2001). Carcinogenicity has not been evaluated by IARC or US EPA. Molybdenum by the oral route has low toxicity. There is some evidence of carcinogenicity in the mouse when molybdenum is administered by the inhalation route. The possible carcinogenic effects were considered the endpoint of greatest toxicological relevance for this route of exposure.

PDE – Oral Exposure

A good laboratory practice compliant 90-day toxicology study that investigated the toxicity of sodium molybdate dehydrate administered in the diet of rats demonstrated effects at 60 mg Mo/kg/day, including effects on body weight, weight gain, food conversion efficiency, some organ weights (absolute and relative to body weight) and renal histopathology (slight diffuse hyperplasia in the proximal tubules in 2 females) (Murray *et al*, 2014). No adverse effects were noted after a 60-day recovery period, with the exception of reduced body weights in male rats. No adverse effects on reproductive organs, estrus cycles, or sperm parameters were noted. The authors conclude that the NOAEL for this study was 17 mg Mo/kg/day. No treatment-related toxicity was seen at this dose. Using modifying factors (F1-F5 as discussed in Appendix 1) the oral PDE is:

PDE = 17 mg/kg x 50 kg / 5 x 10 x 5 x 1 x 1 = 3.4 mg/d = 3400 µg/day

PDE – Parenteral Exposure

In Vyskocil and Viau (1999), it was reported that oral bioavailability in humans ranged from 28-77%. Turnland *et al.* (2005) report that molybdenum absorption was about 90% in healthy men. Therefore, the parenteral PDE is divided by a modifying factor of 2 (as described in Section 3.1).

PDE= 3400 µg/day / 2 = 1700 µg/day

PDE – Inhalation Exposure

Inhaled molybdenum trioxide was carcinogenic in male and female mice (NTP, 1997) and the weight of evidence suggests that calcium and zinc molybdates may be carcinogenic to humans (NAS, 2000). Modeling was conducted using the adenoma/carcinoma incidence data (combined) in female mice (3/50, 6/50, 8/49, and 15/49 for the 0, 10, 30 and 100 mg/m^3 exposure groups, respectively) to determine a linear extrapolation, the unit risk of lung cancer is less than 2.6×10^{-5}/µg/m^3 (NAS, 2000). Using a risk level of 1:100000, the inhalation PDE is calculated as follows:

$$\text{Inhalation PDE} = \frac{1\text{x}10^{-5}}{2.6\ \text{x}10^{-5}\ /\mu\text{g/m}^3} = 0.38\ \mu\text{g/m}^3$$

PDE = 0.38 µg/m^3 / 1000 L/m^3 x 28800 L/d = 10.9 µg/day

No modifying factors are used to adjust a PDE derived by the unit risk approach.

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Nickel

Summary of PDE for Nickel

Nickel (Ni)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	220	22	6.0

Introduction

Nickel (Ni) is a Group 10 element of the first transition series. Although nickel may exist in the 0, +1, +2 and +3 oxidation states, its main oxidation state is +2. Nickel is a naturally occurring metal existing in various mineral forms. In general, nickel compounds are grouped based on solubility in water, and the more soluble nickel compounds, including nickel chloride, nickel sulfate, and nickel nitrate, tend to be more toxic than less soluble forms, such as nickel oxide and nickel subsulfide (ATSDR, 2005). Nickel is nutritionally not essential for humans, but nickel deficiency may cause adverse effects in animals. Nickel as Ni-Al alloys is being used as catalyst in hydrogenation reactions. Stainless steel, which may be used in metered-dose inhaler components, is an iron-based alloy containing chromium and may also contain <1-38% nickel as an oxide (Stockmann-Juvala *et al*, 2013; NTP, 2006). Daily intake of nickel ranges from 100-300 µg/day (US EPA, 1996).

Safety Limiting Toxicity

Nickel is genotoxic, but not mutagenic (IARC 2012). There is no indication of carcinogenicity of Ni salts after oral administration (Heim *et al*, 2007). Depending on the type of salt there was an increase in tumors in some rodent inhalation studies (ATSDR, 2005; EU EFSA, 2005). The US EPA has concluded that there is sufficient evidence of carcinogenicity of nickel refinery dust (US EPA, 2012). In contrast to nickel refinery dust, no significant increase in cancer risk was found in workers in nickel alloy or stainless steel production (ATSDR, 2005). Combining all forms of nickel, IARC (2012) classified nickel as a human carcinogen (Group 1).

In humans and animals, ingestion of large amounts of nickel may cause stomach pain, depression of body weight and adverse effects on blood and kidneys. Humans generally become sensitized to nickel after prolonged contact with the skin. Human data show that an oral challenge to a single dose of nickel administered in drinking water can induce dermatitis in nickel-sensitized individuals (Nielsen *et al*, 1999). In the derivation of the oral reference dose (US EPA, 1996) for soluble salts of nickel, individuals with nickel hypersensitivity were not taken into account. Chronic inhalation may produce adverse changes such as inflammation in lung and nasal cavity in both humans and animals; bronchitis, emphysema, fibrosis and impaired lung function have been reported in nickel welders and foundry workers (ATSDR, 2005). The inflammatory lung lesions which developed in rats administered the soluble $NiSO_4$ were qualitatively similar, but less severe than those occurring in rats administered the insoluble NiO (Benson, 1995). The toxicity of nickel appears greater for soluble forms, which are more rapidly absorbed from the lung (Schaumlöffel, 2012).

PDE – Oral Exposure

In a 2-year carcinogenicity study in rats administered nickel sulfate hexahydrate at 10, 30 or 50 mg/kg/day, no treatment-related tumors were observed. There was a significant exposure-response in mortality in females during weeks 0-105 at all dose levels, and a dose-dependent decrease in body weights in both sexes at week 103 that reach significance in the 30 and 50 mg/kg/day groups (Heim *et al*, 2007). Using the LOAEL of 10 mg/kg/day (2.2 mg Ni/kg/d), and taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral PDE is:

PDE = 2.2 mg/kg/d x 50 kg / 5 x 10 x 1 x 1 x 10 = 0.22 mg/d = 220 µg/day

A factor of 10 was chosen for F5 because a LOAEL was used to set the PDE.

PDE – Parenteral Exposure

A human study using a stable nickel isotope estimated that 29-40% of the ingested label was absorbed (based on fecal excretion data) (Patriarca *et al.* 1997). In another study assessing the effect of food on nickel absorption, between 2-23% of an administered dose was absorbed (Nielsen *et al*, 1999). Therefore, on the basis of limited oral bioavailability of nickel and water-soluble nickel compounds, the parenteral PDE was calculated by dividing the oral PDE by a modifying factor of 10 (as described in Section 3.1).

PDE = 220 µg/d / 10 = 22 µg/day

PDE – Inhalation Exposure

For calculation of the inhalation PDE, a relevant form of nickel was selected from the available data. In 2-year studies with nickel oxide, no tumors were observed in hamsters (Wehner *et al.* 1984) or mice (NTP, 2006). There was some evidence of carcinogenicity in rats (NTP, 2006) but no evidence of carcinogenicity with inhalation of metallic nickel (Oller *et al*, 2008). For nickel, the modifying factor approach was considered acceptable because the forms and levels likely to be in inhalation drug products have not shown evidence of carcinogenicity. Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the inhalation PDE is calculated based on the NOAEL in the rat study of 0.5 mg Ni/m^3 /day.

$$\text{For continuous dosing} = \frac{0.5\ \text{mg/m}^3 \times 6\ \text{hr/d} \times 5\ \text{d/wk}}{24\ \text{hr/d} \times 7\ \text{d/wk}} = \frac{0.089\ \text{mg/m}^3}{1000\text{L/m}^3} = 0.000089\ \text{mg/L}$$

$$\text{Daily dose} = \frac{0.000089\ \text{mg/L} \times 290\ \text{L/d}}{0.425\ \text{kg bw}} = 0.060\ \text{mg/kg}$$

PDE = 0.060 mg/kg x 50 kg / 5 x 10 x 1 x 10 x 1 = 6.0 µg/day

A factor of 10 was chosen for F4 because of the potential of relatively insoluble forms of Ni to accumulate in the lungs and that inflammation was observed in the lungs upon histopathology after inhalation of all forms of Ni.

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Palladium

Summary of PDE for Palladium

Palladium (Pd)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	100	10	1.0

Introduction

Palladium (Pd) is a steel-white, ductile metallic element resembling and occurring with the other platinum group metals and nickel. It exists in three states: Pd(0) (metallic), Pd(2+) and Pd(4+). It can form organometallic compounds, only few of which have found industrial uses. Palladium (on various supports) is being used as catalyst in hydrogenation reactions. Palladium metal is stable in air and resistant to attack by most reagents except aqua regia and nitric acid.

Safety Limiting Toxicity

In a 90-day study in male rats administered 10, 100 and 250 ng/mL palladium in drinking water, palladium was found to accumulate in the kidney but not liver, lung, spleen or bones. Elimination was primarily through the fecal route (Iavicoli *et al*, 2010). Several *in vitro* mutagenicity tests of different palladium compounds with bacterial or mammalian cells (Ames test with *Salmonella typhimurium*; SOS chromotest with *Escherichia coli*; micronucleus test with human lymphocytes) gave negative results (IPCS, 2002; Kielhorn *et al*, 2002). The data was reviewed to identify the safety limiting toxicities based on routes of administration.

PDE – Oral Exposure

Several long-term animal studies have been conducted exploring the toxicity and carcinogenicity of palladium salts. However, none to date have been executed in accordance with current guidelines for toxicological studies. The available data suggest potential NOAELs for palladium in the range of 0.8-1.5 mg/kg. A lifetime study with mice given Pd(2+) chloride in drinking-water at a dose of about 1.2 mg Pd/kg/day found a significantly higher incidence of amyloidosis in several inner organs of males and females and suppressed growth in males, but not in females (Schroeder and Mitchener, 1971; IPCS, 2002). This study also contained a signal that suggested a possible carcinogenic endpoint; however, the design of the study (single dose level, pooling of the tumor rates from male and female animals, and a significant increase in the age of the treated *vs* control animals) limited the utility of the data to assess the carcinogenic potential. Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral PDE is calculated based on the LOEL of 1.2 mg/kg/day.

PDE = 1.2 mg/kg/d x 50 kg / 12 x 10 x 1 x 1 x 5 = 0.1 mg/d = 100 µg/day

A factor of 5 was chosen for F5 because a LOEL was used in deriving the PDE.

PDE – Parenteral Exposure

The safety review for palladium was unable to identify any significant assessments upon which to calculate a PDE for parenteral routes of exposure. Pd(2+) chloride ($PdCl_2$) was poorly absorbed from the digestive tract (<0.5% of the initial oral dose in adult rats or about 5% in suckling rats after 3-4 days). Absorption/retention in adult rats was higher following intratracheal or intravenous exposure, resulting in total body burdens of 5% or 20%, respectively, of the dose administered, 40 days after dosing (IPCS, 2002). On the basis of limited oral bioavailability of palladium, the parenteral PDE was calculated by dividing the oral PDE by a modifying factor of 10 (as described in Section 3.1).

PDE = 100 µg/d / 10 = 10 µg/day

PDE – Inhalation Exposure

There are no adequate inhalation data on Pd. Therefore, the inhalation PDE was calculated by dividing the oral PDE by a modifying factor of 100 (as described in Section 3.1).

PDE = 100 µg/d / 100 = 1.0 µg/day

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Platinum

Summary of PDE for Platinum

Platinum (Pt)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	108	10.8	1.4

Introduction

Platinum (Pt) is a Group 8 element of the third transition series. It is the most important of the six heaviest of the Group 8 elements, collectively called the "platinum group metals" or "platinoids", including palladium, osmium, rhodium, ruthenium and iridium. Metallic platinum has been shown to catalyze many oxidation-reduction and decomposition reactions and the major industrial use of platinum is as a catalyst. Platinum complexes exhibiting a range of oxidation states are known, although the principal oxidation states are +2 and +4. Pt(2+) forms a tetra-coordinate aqua ion $[Pt(H_2O)_4]^{2+}$. The most common Pt IV catalysts are chloroplatinate salts such as tetra and hexachloroplatinate ions.

Safety Limiting Toxicity

No experimental data are available on the carcinogenicity of platinum and platinum compounds forms likely to be present in pharmaceuticals as impurities, and toxicology data are limited (US EPA, 2009).

Chlorinated salts of platinum are responsible for platinum related hypersensitivity and are a major occupational health concern (US EPA, 2009). The hypersensitivity appears to be the most sensitive endpoint of chloroplatinate exposure, at least by the inhalation route. Signs include urticaria, contact dermatitis of the skin, and respiratory disorders ranging from sneezing, shortness of breath, and cyanosis to severe asthma (IPCS, 1991). Exposure reduction was effective in resolving symptoms (Merget *et al*, 2001). Neutral complexes and complexes without halogenated ligands do not appear allergenic (US EPA, 2009; EU SCOEL, 2011). The risk of hypersensitivity appears to be related to sensitizing dose and dose and length of exposure (IPCS, 1991; US EPA, 2009; Arts *et al*, 2006) and cigarette smoking (US EPA, 2009; Merget *et al*, 2000; Caverley *et al*, 1995). The data was reviewed to identify the safety limiting toxicities based on routes of administration

PDE – Oral Exposure

In a study in male rats administered $PtCl_2$ (relatively insoluble) and $PtCl_4$ (soluble) in the diet for 4 weeks, no effects were observed on hematological and clinical chemistry parameters for $PtCl_2$. Plasma creatinine was increased and a reduction in hematocrit and erythrocyte parameters was observed in animals dosed with 50 mg Pt/kg diet for four weeks in the form of $PtCl_4$, the highest dose tested. Platinum concentrations increased in tissues in animals dosed with either compound, particularly the kidney (Reichlmayr-Lais *et al*, 1992). This study was used in the determination of the PDE because toxicity is observed in the kidney with platinum compounds and was a main site of accumulation in this study. Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral PDE is calculated based on the NOAEL of 10 mg Pt/kg diet (4.1 mg Pt taken over 28 days; 0.146 mg/d). The body weight of the rats was 35 g at the beginning of the study and the average weight gain over the course of the study was 235 g. A mean body weight of 135 g was used in the calculation.

0.146 mg/d / 0.135 kg = 1.08 mg/kg/day

PDE = 1.08 mg/kg/d x 50 kg / 5 x 10 x 10 x 1 x 1 = 108 µg/day

PDE – Parenteral Exposure

The safety review for platinum identified limited assessments of platinum salt toxicity for parenteral routes of administration. The oral absorption of platinum salts is very low in rats (<1% when administered by gavage) and higher in humans (42-60% of dietary Pt; US EPA, 2009). Therefore, the oral PDE is divided by a factor of 10 (as described in Section 3.1) to obtain the parenteral PDE.

PDE = 108 µg/d / 10 = 10.8 µg/day

PDE – Inhalation Exposure

Due to the use of the chloroplatinates in catalytic converters, numerous animal (Biagini *et al*, 1983) and human (Pepys *et al*, 1972; Pickering 1972; Merget *et al*, 2000; Cristaudo *et al.*, 2007) studies have been conducted. The US EPA (1977; 2009) and the European Scientific Committee on Occupational Exposure Limits (EU SCOEL, 2011) have also examined the safety of chloroplatinates based on sensitization. The European Scientific Committee on Occupational Exposure Limits (EU SCOEL) concluded that the database does not allow for setting an occupational limit for soluble platinum salts. The US DoL (2013) has established an occupational limit for soluble platinum salts at 2 $\mu g/m^3$. Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the inhalation PDE is calculated as:

$$\text{For continuous dosing} = \frac{2\ \mu g/m^3 \times 8\ hr/d \times 5\ d/wk}{24\ hr/d \times 7\ d/wk} = \frac{0.48\ \mu g/m^3}{1000\ m^3/L} = 0.00048\ \mu g/L$$

$$\text{Daily dose} = \frac{0.00048\ \mu g/L \times 28800\ L/d}{50\ kg} = 0.27\ \mu g/kg/day$$

PDE = 0.27 µg/kg/d x 50 kg / 1 x 10 x 1 x 1 x 1 = 1.4 µg/d

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Platinum-Group Elements

Summary of PDE for Platinum-Group Elements

Iridium (Ir), Osmium (Os), Rhodium (Rh), Ruthenium (Ru)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	100	10	1.0

Introduction

There is limited toxicological data for the Platinum-Group Elements (PGE) other than platinum, and, to a lesser extent, palladium. Occupational exposure to the PGE may cause hypersensitivity with respiratory symptoms and contact dermatitis (Goossens *et al*, 2011). Acute LD_{50}s are available for some of the platinum-group elements but this information was not sufficient for setting a PDE; longer term toxicology studies are not available. RuO_4 appears to be a stronger oxidizing agent than OsO_4, at least when used in fixing tissues (Gaylarde and Sarkany, 1968; Swartzendruber *et al*, 1995). It appears that the soluble salts of the PGE are more toxic than the metal (Wiseman and Zereini, 2009).

Based on the lack of information on toxicity of the PGE, the PDEs for all routes of administration are based on the palladium PDEs rather than platinum as the more conservative approach. The limited safety information for the PGE is described below.

Safety Evaluation

There are very few published data on the safety of Iridium, Osmium, Rhodium and Ruthenium.

- Iridium
  - Iridium induced DNA single strand breaks in rat fibroblasts as measured in a Comet assay when fibroblasts were incubated with Ir(3+) chloride hydrate for 24 hours No strand breaks were seen after a 2 hour incubation (Iavicoli *et al*, 2012).
  - Groups of Wistar rats were administered Ir(3+) chloride hydrate in drinking water (0, 0.019, 0.19, 1.9, 9.5 and 19 µg Ir/d) for 90 days to assess nephrotoxicity Iavicoli *et al*, 2011). While there may have been some indication of renal toxicity from 0.19 µg/d, this study was not adequate to set an oral PDE.
- Osmium
  - Osmium tetroxide is not very soluble in water (Luttrell and Giles, 2007). Metallic osmium is not toxic (McLaughlin *et al*, 1946).
  - Osmium tetroxide has been used as a treatment for arthritis. As a vapor, OsO_4 can cause severe eye damage and irritation to the eye, nose, throat and bronchial tubes, lung, skin, liver and kidney damage (USDoL, 1978; Luttrell and Giles, 2007).
  - The Permitted Exposure Limit (PEL) TWA for osmium tetroxide (as osmium) is 0.002 mg/m^3 (UsD0L, 2013).
- Rhodium
  - Rh salts (K_2RhCl_5, $(NH_4)_3RhCl_6$) were genotoxic in *Salmonella typhimurium* (Bünger *et al*, 1996). In this assay, rhodium was similar to palladium in terms of cytotoxicity and genotoxicity and much less toxic than platinum. Rhodium induced DNA single strand breaks in rat fibroblasts as measured in a Comet assay when fibroblasts were incubated with Rh(3+) chloride hydrate for 2 or 24 hours (Iavicoli *et al*, 2012). $RhCl_3$ was genotoxic in the human

lymphocyte micronucleus assay and increased DNA migration (Comet assay) in white blood cells (Migliore *et al*, 2002).

  - In a lifetime carcinogenicity bioassay in mice administered rhodium chloride, a higher incidence of tumors in treated animals compared to controls was noted at a dose of 5 ppm in drinking water. The data on tumors were too limited to allow a conclusion of carcinogenicity, a, similar to palladium (Schroeder and Mitchener, 1971).
  - The PEL TWA for rhodium (as Rh) metal fume and insoluble compounds is 0.1 mg/m^3. The PEL TWA for soluble compounds of Rh is 0.001 mg/m^3 (UsD0L, 2013).

- Ruthenium
  - Several Ru complexes cause genotoxic responses *in vitro* in *Salmonella typhimurium* strains TA98 and TA100 (Monti-Bragadin *et al*, 1975; Yasbin *et al*, 1980; Benkli *et al*, 2009).
  - Oral absorption of Ru is low (about 4%); the half-life of a parenteral dose is about 200 days. Ingested ruthenium compounds are retained in bones (Furchner *et al*, 1971).

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Selenium

Summary of PDE for Selenium

Selenium (Se)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	170	85	135

Introduction

Selenium (Se) is present in the earth's crust, often in association with sulfur-containing minerals. It can assume four oxidation states (-2, 0, +4, +6) and occurs in many forms, including elemental selenium, selenites and selenates. Selenium is an essential trace element for many species, including humans. Selenium is incorporated into proteins *via* a specific selenocysteine tRNA. Selenium is being used as a catalyst in the manufacture of rubber. Ru-Se catalysts are used in oxygen reduction. Aryl- and alkyl-Selenium reagents have various applications in organic synthesis.

Safety Limiting Toxicity

Selenium was listed as a Group 3 compound (not classifiable for carcinogenesis) by IARC (1987). The only selenium compound that has been shown to be carcinogenic in animals is selenium sulfide (NTP, 1980). According to the US EPA, selenium sulfide is in Group B2 (probable human carcinogen) (US EPA, 2002). Other selenium compounds are classified as D; not classifiable as to carcinogenicity in humans.

The most significant toxicity observed with excessive exposure in humans to Se is selenosis, characterized primarily by dermal and neurological effects, including unsteady gait and paralysis (ATSDR, 2003). There is some concern over exposure to excessive levels of selenium in the diet; to limit the total exposure to Se, various organizations have set an upper tolerable limit at 400 µg/day (WHO, 2011). Occupational studies describe respiratory effects such as irritation of the nose, respiratory tract, and lungs, bronchial spasms, and coughing following chronic exposure to selenium dioxide or elemental selenium as dust. Respiratory symptoms similar to those reported for occupationally-exposed humans have been seen in animals inhaling high doses of elemental selenium fumes or dust, and studies of animals with acute inhalation exposure to hydrogen selenide or elemental selenium fumes or dust have reported hepatocellular degeneration and atrophy of the liver. Absorption after inhalation exposure is uncertain (ATSDR, 2003).

PDE – Oral Exposure

In a rat carcinogenicity study of selenium sulfide, the NOAEL for hepatocellular carcinoma was 3 mg/kg/day (1.7 mg Se/kg/day) (NTP, 1980). Although, there is insufficient data to assess carcinogenicity of other forms of selenium, and the human relevance of the rodent liver tumors has been questioned (IARC, 1999), this is the best available study. Some human data are available but only in a limited number of subjects (ATSDR, 2003). The calculated PDE is in line with the MRL of 5 µg/kg/day for Se (ATSDR, 2003). Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral PDE is calculated as below.

PDE = 1.7 mg/kg/d x 50 kg / 5 x 10 x 1 x 10 x 1 = 170 µg/day

A factor of 10 was chosen for F4 because of the risk of selenosis.

PDE – Parenteral Exposure

Studies in humans and experimental animals indicate that, when ingested, several selenium compounds including selenite, selenate, and selenomethionine are readily absorbed, often to greater

than 80% of the administered dose (ATSDR, 2003). On the basis of oral bioavailability of ~80%, the parenteral PDE was calculated by dividing the oral PDE by a modifying factor of 2 (as described in Section 3.1).

PDE = 170 µg/d / 2 = 85 µg/day

PDE – Inhalation Exposure

Respiratory endpoints are the most sensitive markers for inhalation exposure in occupational studies. Occupational limits have established time weighted averages for selenium exposures of 0.2 mg/m^3 (US DoL, 2013) and 0.07 by the European Union Scientific Expert Group (EU SEG, 1992). However, the EU SEG Occupation Exposure Limits (OEL) was based on hydrogen selenide, a form not likely to be present in inhalation products. Thus, using the OEL derived by US DoL, and taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the inhalation PDE is calculated as below.

$$\text{For continuous dosing} = \frac{0.2\ \text{mg/m}^3\ 8\ \text{hr/d} \times 5\ \text{d/wk}}{24\ \text{hr/d} \times 7\ \text{d/wk}} = \frac{0.048\ \text{mg/m}^3}{1000\ \text{L/m}^3} = 0.000048\ \text{mg/L}$$

$$\text{Daily dose} = \frac{0.000048\ \text{mg/L} \times 28800\ \text{L}}{50\ \text{kg}} = 0.027\ \text{mg/kg}$$

PDE = 0.027 mg/kg x 50 kg / 1 x 10 x 1 x 1 x 1= 0.135 mg/day =135 µg/day

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Silver

Summary of PDE for Silver

Silver (Ag)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	167	14	7.0

Introduction

Silver (Ag) is present in silver compounds primarily in the +1 oxidation state and less frequently in the +2 oxidation state. Silver occurs naturally mainly in the form of very insoluble and immobile oxides, sulfides and some salts. The most important silver compounds in drinking-water are silver nitrate and silver chloride. Most foods contain traces of silver in the 10–100 µg/kg range. Silver is nutritionally not essential and no metabolic function is known. Silver is being used as a catalyst in the oxidation of ethylene to ethylene oxide. Silver-Cadmium alloy is used in selective hydrogenation of unsaturated carbonyl compounds. Silver oxide is used as a mild oxidizing agent in organic synthesis.

Safety Limiting Toxicity

Silver is not mutagenic. Animal toxicity studies and human occupational studies have not provided sufficient evidence of carcinogenicity. Based on these data silver is not expected to be carcinogenic in humans (ATSDR, 1990).

Argyria appears to be the most sensitive clinical effect in response to human Ag intake. Silver acetate lozenges are used in smoking cessation (Hymowitz and Eckholdt, 1996). Argyria, a permanent bluish-gray discoloration of the skin, results from the deposition of Ag in the dermis combined with an silver-induced production of melanin. Inhalation of high levels of silver can result in lung and throat irritation and stomach pains (ATSDR, 1990).

PDE – Oral Exposure

Silver nitrate was added at 0.015% to the drinking water of female mice (0.9 g/mouse; 32.14 mg/kg silver nitrate; 64% silver) for 125 days to examine neurobehavioral activity of the animals based on potential neurotoxicity of silver (Rungby and Danscher, 1984). Treated animals were hypoactive relative to controls; other clinical signs were not noted. In a separate study, silver was shown to be present in the brain after mice were injected with 1 mg/kg intra peritoneal silver lactate (Rungby and Danscher, 1983). The oral PDE is consistent with the reference dose of 5 µg/kg/day (US EPA, 2003). Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral PDE is calculated as below.

PDE = 20 mg/kg x 50 kg / 12 x 10 x 5 x 1 x 10 = 167 µg/day

A factor 10 was chosen for F5 because the LOAEL was used to set the PDE as few toxicological endpoints were examined.

PDE – Parenteral Exposure

US EPA (2003) identified a LOAEL of 0.014 mg/kg Ag/day using long-term (2 to 9 years) human intravenous data based on argyria following colloidal and organic silver medication. Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the parenteral PDE is calculated as below.

PDE = 0.014 mg/kg/d x 50 kg / 1 x 10 x 1 x 1 x 5 = 14 µg/day

A factor of 5 was chosen for F5 as the finding of argyria was considered a LOEL because accumulation of silver in the skin is not considered adverse.

PDE – Inhalation Exposure

Lung and throat irritation and stomach pains were the principal effects in humans after inhalation of high Ag levels. Using the Threshold Limit Value (TLV) of 0.01 mg/m^3 for silver metal and soluble compounds (US DoL, 2013), and taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the inhalation PDE is calculated as:

$$\text{For continuous dosing} = \frac{0.01\ mg/m^3\ 8\ hr/d \times 5\ d/wk}{24\ hr/d \times 7\ d/wk} = \frac{0.0024\ mg/m^3}{1000\ L/m^3} = 0.00000238\ mg/L$$

$$\text{Daily dose} = \frac{0.0000024\ mg/L \times 28800\ L/d}{50\ kg} = 0.0014\ mg/kg/day$$

PDE = 0.0014 mg/kg x 50 kg / 1 x 10 x 1 x 1 x 1= 0.007 mg/d = 7.0 µg/day

REFERENCES

ATSDR. Toxicological Profile for Silver. Agency for Toxic Substances and Disease Registry, Public Health Service, U.S. Department of Health and Human Services, Atlanta, GA. 1990.

Hymowitz N, Eckholt H. Effects of a 2.5-mg silver acetate lozenge on initial and long-term smoking cessation. Prev Med 1996;25:537-46.

Rungby J, Danscher G. Hypoactivity in silver exposed mice. Acta Pharmacol Toxicol 1984;55:398-401.

Rungby J, Danscher G. Localization of exogenous silver in brain and spinal cord of silver exposed rats. Acta Neuropathol 1983;60(1-2):92-8.

US DoL (OHSA). 29 CRF 1910.1000 Table Z-1. Limits for air contaminants. U.S. Department of Labor. 2013.

US EPA. Silver (CASRN 7440-22-4). Integrated Risk Information System (IRIS). 2003.

Thallium

Summary of PDE for Thallium

Thallium (Tl)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	8.0	8.0	8.0

Introduction

Pure thallium (Tl) is a bluish-white metal. It exists primarily in two oxidation states: +1 and +3. Monovalent thallium is similar to potassium (K+) in ionic radius and electrical charge, which contributes to its toxic nature. Many of the thallium salts are soluble in water with the exception of the insoluble Tl(3+) oxide. Thallium sulfate has been used in medicine, primarily as a depilatory agent, but also to treat infections, such as venereal diseases, ringworm of the scalp, typhus, tuberculosis, and malaria. Tl(3+) salts are being used in organic synthesis. Thallium is nutritionally not essential and no metabolic function is known (ATSDR, 1992).

Safety Limiting Toxicity

In humans and animals, the skin, especially the hair follicles, appears to be the most sensitive target of toxicity from repeated oral exposure to thallium (US EPA, 1992; US EPA, 2009). Water soluble salts (sulphate, acetate, or carbonate) have higher toxicity than other forms (Moore *et al*, 1993).

PDE – Oral Exposure

The primary target organ for oral exposure to thallium in humans and animals appears to be the skin, especially the hair follicles, as shown in a 90-day toxicity rat study with thallium sulfate. The NOAEL was defined at 0.04 mg Tl/kg on the basis of an increased incidence of alopecia at the higher doses (OEHHA, 1999; US EPA, 2009). Thus, the oral PDE was determined on the basis of the NOAEL of 0.04 mg Tl/kg in rat.

Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral PDE is calculated as below.

PDE = 0.04 mg/kg/d x 50 kg / 5 x 10 x 5 x 1 x 1 = 0.008 mg/day = 8.0 µg/day

PDE – Parenteral Exposure

No relevant data on parenteral exposure to thallium compounds were found. The bioavailability of soluble thallium salts is high (> 80%) (US EPA, 2009). Therefore, the parenteral PDE is the same as the oral PDE.

PDE = 8.0 µg/day

PDE – Inhalation Exposure

No relevant data on inhalation exposure to thallium compounds were found. The US EPA concluded that information on the inhalation toxicity of thallium is insufficient to derive an inhalation reference concentration. Occupational epidemiology studies involving possible inhalation exposures to thallium were limited and inconclusive (US EPA, 2009). The major toxicity identified in humans and animals is alopecia, and absorption and toxicity is considered high by the inhalation route (IPCS, 1996). Similar findings may be expected by Tl exposure *via* oral and respiratory routes. For this reason, the inhalation PDE is set at the parenteral PDE.

PDE = 8.0 µg/day

REFERENCES

ATSDR. Toxicological profile for thallium. Agency for Toxic Substances and Disease Registry, Public Health Service, U.S. Department of Health and Human Services, Atlanta, GA. 1992.

IPCS. Thallium and thallium salts: health and safety guide. International Programme on Chemical Safety, World Health Organization, Geneva, 1996. Health and Safety Guide No. 102.

Moore D, House I, Dixon A. Thallium poisoning. Br Med J 1993;306:1527-9.

OEHHA. Public health goal for thallium in drinking water. Office of Environmental Health Hazard Assessment, Berkeley and Sacramento, CA. 1999.

US EPA. Drinking water criteria document for thallium. Health and Ecological Criteria Division; Office of Science and Technology; Office of Water; U.S. Environmental Protection Agency, Washington DC, 1992.

US EPA. Toxicological review of thallium and compounds (CAS No. 7440-28-0). Integrated Risk Information System (IRIS). 2009. EPA/635/R-08/001F

Tin

Summary of PDE for Tin

Tin (Sn)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	6400	640	64

Introduction

Tin (Sn) is a silvery-white metal that exists in +2 and +4 oxidation states. The most important inorganic compounds of tin are its oxides, chlorides, fluorides and halogenated sodium stannates and stannites. Tin is present in some multi-vitamin and mineral food supplements (at levels up to 10 µg Sn/tablet). Tin is possibly nutritionally essential for some animals, but it has not been shown to be essential for humans. Tin(2+) chloride is being used as a reducing agent, and as a stabilizer of polyvinylchloride (PVC). This safety assessment focuses on inorganic tin considering that the more frequent occurrence of inorganic tin is more relevant with respect to metal impurities in drug products than organic tin compounds.

Safety Limiting Toxicity

There is no indication of *in vivo* genotoxicity or carcinogenicity for tin and tin salts. In several studies in rats, a decrease in hemoglobin as an early sign for anemia was the most sensitive endpoint. In general, in *in vitro* assays tin and tin salts were negative for mutagenicity but some forms were positive for chromosomal damage (CICAD, 2005). Stannous chloride was not carcinogenic in the two year assay in mice or rats (NTP, 1982).

PDE – Oral Exposure

Anemia was the most sensitive endpoint in rats after repeated oral administration. Thus, the PDE for oral exposure was determined on the basis of the lowest NOAEL, i.e., 150 ppm (equivalent to 32 mg Sn/kg/day; ATSDR, 2005). This value was obtained from a 90-day study in rats based on signs of anemia starting at 500 ppm in rats exposed to stannous chloride *via* diet (de Groot *et al*, 1973). This study was considered more relevant than the NTP study (NTP, 1982) in determining the oral PDE because in the 13-week NTP dose range finding study, the toxicological evaluation was more limited (e.g., no clinical chemistry, including effects on hemoglobin) than in the study by de Groot *et al.* Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral PDE is calculated as below.

PDE = 32 mg/kg/d x 50 kg / 5 x 10 x 5 x 1 x 1 = 6.4 mg/d = 6400 µg/day

PDE – Parenteral Exposure

The safety review for tin was unable to identify any significant assessments upon which to calculate a PDE for parenteral routes of exposure. On the basis of an oral bioavailability of about 5% for tin and inorganic tin compounds (ATSDR, 2005), the parenteral PDE was calculated by dividing the oral PDE by a modifying factor of 10 (as described in Section 3.1).

PDE = 6400 µg/d / 10 = 640 µg/day

PDE – Inhalation Exposure

The safety review for tin was unable to identify any significant assessments on inorganic tin upon which to calculate a PDE for inhalation routes of exposure. Although a TLV is available for tin (2 mg/m^3; US DoL, 2013), there is insufficient data to set a MRL (ATSDR 2005; EU SCOEL 2003).

Therefore, the PDE for tin is calculated by using a factor of 100 to convert the oral PDE to the inhalation PDE (as described in Section 3.1).

PDE = 6400 µg/d / 100 = 64 µg/day

REFERENCES

ATSDR. Toxicological profile for tin and tin compounds. Agency for Toxic Substances and Disease Registry, Public Health Service, U.S. Department of Health and Human Services, Atlanta, GA. 2005.

CICAD. Tin and inorganic compounds. Concise International Chemical Assessment Document. World Health Organization, Geneva, 2005. Document 65.

De Groot AP, Feron V, Til H. Short-term toxicity studies on some salts and oxides of tin in rats. Food Cos Toxicol 1973;11:19-30.

EU SCOEL. Recommendation from the scientific committee on occupational exposure limits for tin and inorganic tin compounds. European Union Scientific Committee on Occupational Exposure Limits. 2003;SCOEL/SUM/97.

NTP. Technical report on the carcinogenesis bioassay of stannous chloride (CAS NO. 7772-99-8) in F344/N and B6C3F$_1$/N mice (feed study). National Toxicology Program. U.S. Department of Health and Human Services. 1982; Technical Report Series No. 231.

US DoL (OHSA). 29 CRF 1910.1000 Table Z-1. Limits for air contaminants. U.S. Department of Labor. 2013.

Vanadium

Summary of PDE for Vanadium

Vanadium (V)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	120	12	1.2

Introduction

Vanadium (V) is present as a trace element in the earth's crust and can exist in a variety of oxidation states (-1, 0, +2, +3, +4 and +5). V is also present in trace quantities in most biological organisms with the principal ions being vanadate, VO_3^- and vanadyl, VO_2^+. Absorption of vanadium from the gastrointestinal tract is poor. Estimates of total dietary intake of vanadium in humans range from 10 to 60 µg/day. Intake from drinking water depends on the water source and estimates are up to 140 µg/day. Human populations have variable serum concentrations of vanadium, with 2 µg/L being the high end of the normal range. Despite its being ubiquitous in the body, an essential biological role for vanadium in humans has not been established.

Safety Limiting Toxicity

Vanadium is genotoxic, but not mutagenic (ATSDR, 2012). Vanadium pentoxide is classified as a possible human carcinogen (Group 2B; IARC, 2012).

PDE – Oral Exposure

Following oral administration to animals and humans the gastrointestinal tract, cardiovascular, and hematological system are the primary targets of toxicity. The most appropriate study to assess vanadium toxicity through oral administration was conducted in humans exposed to vanadium for 12 weeks. In this study, no significant alterations in hematological parameters, liver function (as measured by serum enzymes), cholesterol and triglyceride levels, kidney function (as measured by blood urea nitrogen), body weight, or blood pressure were observed in subjects administered *via* capsule 0.12 or 0.19 mg vanadium as ammonium vanadyl tartrate or vanadyl sulfate for 6–12 weeks (ATSDR, 2012). The oral NOAEL of 0.12 mg vanadium/kg/day for hematological and blood pressure effects was used to calculate the oral PDE. Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral PDE is calculated as below.

PDE = 0.12 mg/kg/d x 50 kg / 1 x 10 x 5 x 1 x 1 = 0.12 mg/d = 120 µg/day

PDE – Parenteral Exposure

The safety review for vanadium was unable to identify any significant assessments upon which to calculate a PDE for parenteral routes of exposure. On the basis of an approximate oral bioavailability of <1–10% for vanadium and inorganic vanadium compounds (ATSDR, 2012), the parenteral PDE was calculated by dividing the oral PDE by a modifying factor of 10 (as described in Section 3.1).

PDE = 120 µg/day / 10 = 12 µg/day

PDE – Inhalation Exposure

A two year chronic inhalation exposure study in rats was considered for use for the inhalation PDE for vanadium. In this study, carcinogenic effects were observed to the lowest dose tested, 0.5 mg/m^3 vanadium pentoxide (Ress *et al.* 2003). Vanadium pentoxide is a caustic agent and is not considered to be present in drug products. Therefore, the inhalation PDE for vanadium was calculated by dividing the oral PDE by a modifying factor of 100 (as described in Section 3.1).

PDE = 120 µg/d / 100 = 1.2 µg/day

REFERENCES

ATSDR. Toxicological profile for vanadium. Agency for Toxic Substances and Disease Registry, Public Health Service, U.S. Department of Health and Human Services, Atlanta, GA. 2012.

IARC. Arsenic, metals, fibres, and dusts: a review of human carcinogens. Monographs on the Evaluation of Carcinogenic Risks to Humans. International Agency for Research on Cancer, World Health Organization, Lyon. 2012;100C.

Ress NB, Chou BJ, Renne RA, Dill JA, Miller RA, Roycroft JH et al. Carcinogenicity of inhaled vanadium pentoxide in F344/N rats and B6C3F1 mice. Toxicol Sci 2003;74(2):287-96.

Appendix 4: Illustrative Examples

Examples for Converting PDEs into Permitted Elemental Impurity Concentrations

Option 1: Permitted common concentration limits of elemental impurities across drug product component materials for products with daily intakes of not more than 10 grams.

For this example, consider a solid oral drug product with a maximum daily intake of 2.5 grams, containing 9 components (1 drug substance and 8 excipients, see Table A.4.1). Because this drug product does not exceed a maximum daily intake of 10 grams, the concentrations in Table A.2.2 may be used. As Option 1 has a common permitted concentration, the 9 components can be used in any proportion in the formulation. The drug substance synthesis uses Pd and Ni catalysts, and Pb, As, Cd, Hg, and V are also of concern on the basis of the risk assessment. The maximum daily intake of each elemental impurity in the drug product is given in Table A.4.2 assuming that each elemental impurity is present at the concentration given in Table A.2.2. The maximum potential daily intake of an elemental impurity is determined using the actual drug product daily intake and the concentration limit for the elemental impurity in Table A.2.2 (concentration multiplied by the actual daily intake of the drug product of 2.5 grams). The maximum daily intake given for each elemental impurity is not a summation of values found in the individual columns of Table A.4.2.

This calculation demonstrates that no elemental impurities exceed their PDEs. Thus if these concentrations in each component are not exceeded, the drug product is assured to not exceed the PDEs for each identified elemental impurity.

Table A.4.1 Maximum Daily Intake of Components of the Drug Product

Component	Daily Intake, g
Drug Substance	0.200
Microcrystalline Cellulose (MCC)	1.100
Lactose	0.450
Ca Phosphate	0.350
Crospovidone	0.265
Mg Stearate	0.035
Hydroxypropylmethyl Cellulose (HPMC)	0.060
Titanium Dioxide	0.025
Iron Oxide	0.015
Drug Product	2.500

Table A.4.2 Permitted Concentrations from Table A.2.2 (assuming uniform concentrations and 10 grams daily intake)

Component	Maximum Permitted Concentration (µg/g)						
	Pb	As	Cd	Hg	Pd	V	Ni
Drug Substance	0.5	1.5	0.5	3	10	10	20
MCC	0.5	1.5	0.5	3	10	10	20
Lactose	0.5	1.5	0.5	3	10	10	20
Ca Phosphate	0.5	1.5	0.5	3	10	10	20
Crospovidone	0.5	1.5	0.5	3	10	10	20
Mg Stearate	0.5	1.5	0.5	3	10	10	20
HPMC	0.5	1.5	0.5	3	10	10	20

Titanium Dioxide	0.5	1.5	0.5	3	10	10	20
Iron Oxide	0.5	1.5	0.5	3	10	10	20
Maximum Daily intake (µg)	1.25	3.75	1.25	7.5	25	25	50
PDE (µg)	5	15	5	30	100	100	200

Option 2a: Permitted common concentration limits across drug product component materials for a product with a specified daily intake:

For this example, consider the same solid oral drug product with a maximum daily intake of 2.5 grams, containing 9 components (1 drug substance and 8 excipients, see Table A.4.1) used in Option 1. As Option 2a has a common permitted concentration, the 9 components can be used in any proportion in the formulation. The drug substance synthesis uses Pd and Ni catalysts, Pb, As, Cd, Hg, and V are also of concern on the basis of the risk assessment. The maximum concentration of each elemental impurity identified in the risk assessment can be calculated using the PDEs in Table A.2.1 and Equation 1.

The maximum potential daily intake of an elemental impurity is determined using the actual drug product daily intake and the concentration limit for the elemental impurity in Table A.4.3 (concentration multiplied by the actual daily intake of the drug product of 2.5 grams). The maximum daily intake given for each elemental impurity is not a summation of values found in the individual columns of Table A.4.3.

This calculation also demonstrates that no elemental impurities exceed their PDEs. Thus if these concentrations in each component are not exceeded, the drug product is assured to not exceed the PDEs for each identified elemental impurity.

The factor of 4 increase in Option 2a for permitted concentration seen when comparing Option 1 and Option 2a concentration limits is due to the use of 10 grams and 2.5 grams, respectively, as daily intake of the drug product.

Table A.4.3 Calculation of Maximum Permitted Concentrations Assuming Uniform Concentrations in a Product with a Specified Daily Intake:

Component	Maximum Permitted Concentration (µg/g)						
	Pb	As	Cd	Hg	Pd	V	Ni
Drug Substance	2	6	2	12	40	40	80
MCC	2	6	2	12	40	40	80
Lactose	2	6	2	12	40	40	80
Ca Phosphate	2	6	2	12	40	40	80
Crospovidone	2	6	2	12	40	40	80
Mg Stearate	2	6	2	12	40	40	80
HPMC	2	6	2	12	40	40	80
Titanium Dioxide	2	6	2	12	40	40	80
Iron Oxide	2	6	2	12	40	40	80
Maximum Daily intake (µg)	5	15	5	30	100	100	200
PDE (µg)	5	15	5	30	100	100	200

Option 2b: Permitted concentration limits of elemental impurities across drug product component materials for a product with a specified daily intake:

For this example, consider the same solid oral drug product with a maximum daily intake of 2.5 grams, containing 9 components (1 drug substance and 8 excipients, see Table A.4.1) used in Option 1 and 2a. The drug substance synthesis uses Pd and Ni catalysts, and Pb, As, Cd, Hg, and V are also of concern on the basis of the risk assessment. To use Option 2b, the composition of the drug product and additional knowledge regarding the content of each elemental impurity in the components of the drug product are considered. The following table shows example data on elemental impurities that may be derived from the sources described in Section 5.5:

Table A.4.4 Concentrations of Elemental Impurities (µg/g) in the Components

Component	Concentration (µg/g)						
	Pb	As	Cd	Hg	Pd	V	Ni
Drug Substance	<LoQ	0.5	<LoQ	<LoQ	20	<LoQ	50
MCC	0.1	0.1	0.1	0.1	*	<LoQ	<LoQ
Lactose	0.1	0.1	0.1	0.1	*	<LoQ	<LoQ
Ca Phosphate	1	1	1	1	*	10	5
Crospovidone	0.1	0.1	0.1	0.1	*	<LoQ	<LoQ
Mg Stearate	0.5	0.5	0.5	0.5	*	<LoQ	0.5
HPMC	0.1	0.1	0.1	0.1	*	<LoQ	<LoQ
Titanium Dioxide	20	1	1	1	*	1	<LoQ
Iron Oxide	10	10	10	10	*	2000	50

* = The risk assessment determined that Pd was not a potential elemental impurity; a quantitative result was not obtained.

Using the information presented in Table A.4.4, one can evaluate different sets of potential concentrations for each elemental impurity in each component. In table A.4.5, an example of one set of these concentrations is displayed. In this case, a high concentration of lead has been allocated to titanium dioxide and the PDE would not be exceeded due to the low proportion of this component in the drug product, and the low concentrations of lead in the other components. Using these concentrations and the component percent composition (Table A.4.1), levels of elemental impurities in the drug product can be determined using Equation 2 and compared to the established PDE. The concentrations given in Table A.4.5 are only suitable for the component proportions given in Table A.4.1.

Table A.4.5 Example of Potential Concentrations of Elemental Impurities in the Components

Component	Potential Concentration (µg/g)						
	Pb	As	Cd	Hg	Pd	V	Ni
Drug Substance	<LoQ	5	<LoQ	<LoQ	500	<LoQ	750
MCC	0.5	5	1	5	*	<LoQ	<LoQ
Lactose	0.5	5	1	5	*	<LoQ	<LoQ
Ca Phosphate	5	5	5	35	*	70	80
Crospovidone	0.5	5	1	5	*	<LoQ	<LoQ
Mg Stearate	5	10	5	125	*	<LoQ	100
HPMC	2.5	5	1	5	*	<LoQ	<LoQ
Titanium Dioxide	50	40	10	35	*	20	<LoQ

Iron Oxide	50	100	50	200	*	5000	1200

* The risk assessment determined that Pd was not a potential elemental impurity; a quantitative result was not obtained.

Option 3: Finished Product Analysis

For this example, consider the same solid oral drug product with a maximum daily intake of 2.5 grams, containing 9 components (1 drug substance and 8 excipients) used in Option 1, 2a and 2b. The drug substance synthesis uses Pd and Ni catalysts, and Pb, As, Cd, Hg, and V are also of concern on the basis of the risk assessment. The maximum concentration of each elemental impurity in the drug product may be calculated using the daily intake of drug product and the PDE of the elemental impurity using Equation 1. The total mass of each elemental impurity should be not more than the PDE.

Table A.4.6 Calculation of Concentrations for the Finished Product

		Maximum Permitted Concentration (µg/g)						
	Daily Intake (g)	Pb	As	Cd	Hg	Pd	V	Ni
Drug Product	2.5	2	6	2	12	40	40	80
Maximum Daily Intake (µg)		5	15	5	30	100	100	200

Illustrative Example – Elemental Impurities Assessment

The following example is intended as illustration of an elemental impurities risk assessment. This example is intended for illustrative purposes and not as the only way to document the assessment. There are many different ways to approach the risk assessment process and its documentation.

This example relies on the oral drug product described in Appendix 4. Consider a solid oral drug product with a maximum daily intake of 2.5 grams, containing 9 components (1 drug substance and 8 excipients). The drug substance synthesis uses Pd and Ni catalysts.

The applicant conducts the risk assessment starting with the identification of potential elemental impurities following the process described in Section 5. Because the applicant had limited historical data for the excipients used in the drug product, the applicant determined that the Class 1 elements (As, Cd, Hg, Pb) would be taken through the evaluation phase. The table below shows a summary of the findings of the identification stage of the assessment.

Table A.4.7 Identification of Potential Elemental Impurities

	Potential Elemental Impurities			
Component	Intentionally added	Potential elemental impurities with a relatively high abundance and/or are impurities in excipients	Potential elemental impurities from manufacturing equipment	Potential elemental impurities from container closure systems
Drug Substance	Pd, Ni	As	Ni	None
MCC	None	As, Cd, Hg, Pb	None	None
Lactose	None	As, Cd, Hg, Pb	None	None
Ca Phosphate	None	As, Cd, Hg, Pb	V, Ni	None
Crospovidone	None	As, Cd, Hg, Pb	None	None

Mg stearate	None	As, Cd, Hg, Pb	Ni	None
HPMC	None	As, Cd, Hg, Pb	None	None
Titanium Dioxide	None	As, Cd, Hg, Pb	V	None
Iron Oxide	None	As, Cd, Hg, Pb	V, Ni	None

The assessment identified seven potential elemental impurities requiring additional evaluation. Three of the identified elements were found in multiple components. The applicant continued the risk assessment by collecting information from vendors, published literature and data. The individual component data in the risk assessment process is shown below in Table A.4.8. Total daily masses of elemental impurities are calculated as the daily intake of the component times the concentration.

Table A.4.8 Elemental Impurity Assessment – Evaluation of Daily Contribution to the Total Mass of Elemental Impurities in the Drug Product

Component	Daily intake, g	Measured Concentration (µg/g)							Total Daily Mass of Elemental Impurity, µg						
		Pb	As	Cd	Hg	Pd	V	Ni	Pb	As	Cd	Hg	Pd	V	Ni
Drug Substance	0.2	<LoQ	0.5	<LoQ	<LoQ	20	<LoQ	50	0	0.1	0	0	4	0	10
MCC	1.1	0.1	0.1	0.1	0.1	*	<LoQ	<LoQ	0.11	0.11	0.11	0.11	0	0	0
Lactose	0.45	0.1	0.1	0.1	0.1	*	<LoQ	<LoQ	0.045	0.045	0.045	0.045	0	0	0
Ca Phosphate	0.35	1	1	1	1	*	10	5	0.35	0.35	0.35	0.35	0	3.5	1.75
Crospovidone	0.265	0.1	0.1	0.1	0.1	*	<LoQ	<LoQ	0.0265	0.0265	0.0265	0.0265	0	0	0
Mg stearate	0.035	0.5	0.5	0.5	0.5	*	<LoQ	0.5	0.0175	0.0175	0.0175	0.0175	0	0	0.0175
HPMC	0.06	0.1	0.1	0.1	0.1	*	<LoQ	<LoQ	0.006	0.006	0.006	0.006	0	0	0
Titanium Dioxide	0.025	20	1	1	1	*	1	<LoQ	0.5	0.025	0.025	0.025	0	0.025	0
Iron Oxide	0.015	10	10	10	10	*	400	50	0.15	0.15	0.15	0.15	0	6	0.75
TOTAL	2.5 g	-	-	-	-	-	-	-	1.2 µg	0.8 µg	0.7 µg	0.7 µg	4 µg	9.5 µg	12.5 µg

* The risk assessment determined that Pd was not a potential elemental impurity; a quantitative result was not obtained.

The next step in the risk assessment is to compare the measured or predicted levels in the drug product to the control threshold, using the information in Table A.4.8, and determine appropriate actions.

Table A.4.9: Assessment Example – Data Entry Descriptions

Column 1: Review the components of drug product for any elements intentionally added in the production (the primary source is the drug substance). For those used, record the elements for further consideration in the assessment.

Column 2: Identify any potential elements or impurities that are associated with excipients used in the preparation of the drug product. Record the source(s) for further consideration in the assessment.

Column 3: Identify any elemental impurities known or expected to be leached from the manufacturing equipment. Record the specific elemental impurities for further consideration in the assessment.

Column 4: Identify any elemental impurities known or expected to be leached from the container closure system. Record the specific elemental impurities for further consideration in the assessment.

Column 5: Calculate the total contribution of the potential elemental impurity by summing the contributions across the components of the drug product.

Column 6: Assess the variability of the elemental impurity level(s) in the components

Column 7: Enter the control threshold of each potential elemental impurity identified. If the variability is known and it is within acceptable limits, the control threshold (30% of the PDE) for each elemental impurity can be applied.

Column 8: Describe action taken – none if the value in column 5 is less than or equal to the control threshold (Column 7). Define control element if material variability is high or control threshold is exceeded.

	1	2	3	4	5	6	7	8
Element	Intentionally added (if used in the process)	Elemental impurities with a relatively high abundance and/or are impurities in excipients	Manufacturing equipment	Leached from container closure systems	Total elemental impurity contribution µg/	Acceptable variability of elemental impurity contribution	Control threshold	Action
As	No	Observed impurity in all excipients and drug substance	No	No	0.8	yes	4.5	no further controls required
Cd	No	Observed impurity in all excipients	No	No	0.7	yes	1.5	no further controls required
Hg	No	Observed impurity in all excipients	No	No	0.7	yes	9	no further controls required
Pb	No	Observed impurity in all excipients	No	No	1.2	yes	1.5	no further controls required
Pd	API catalyst	No	No	No	4.0	yes	30	no further controls required
Ni	API catalyst	Observed in 3 excipients	No	No	12.5	yes	60	no further controls required
V	No	Observed in 3 excipients	No	No	9.5	yes	30	no further controls required