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GUIDELINE ON THE SPECIFICATION LIMITS FOR RESIDUES OF METAL CATALYSTS OR METAL REAGENTS

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GUIDELINE ON THE SPECIFICATION LIMITS FOR RESIDUES OF METAL CATALYSTS OR METAL REAGENTS

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EXECUTIVE SUMMARY

The objective of this guideline is to recommend maximum acceptable concentration limits for the residues of metal catalysts or metal reagents that may be present in pharmaceutical substances or in drug products. A pharmaceutical substance is defined here as a substance that is either an active pharmaceutical ingredient or an excipient.

The metals addressed in this guideline are normally used as process catalysts or reagents during the synthesis of pharmaceutical substances. Their use may lead to residues in the final pharmaceutical substance, and consequently in the final drug product. Such metal residues do not provide any therapeutic benefit to the patient and should therefore be evaluated and restricted on the foundation of safety- and quality-based criteria. The guideline may be updated to include other metal residues in due course.

This guideline classifies metal residues into three categories based on their individual level of safety concern and sets concentration limits. The limits are based on the maximal daily dose, duration of treatment, and administration route of the drug product as well as the permitted daily exposure (PDE) of the metal residue. The guideline also includes recommendations on testing strategies, analytical procedures and reporting levels in pharmaceutical substances or drug products.

1. INTRODUCTION

Metal residues in pharmaceutical substances or drug products may originate from several sources like metal catalysts and metal reagents used during the synthesis of the active pharmaceutical substance and the excipients, manufacturing equipment and piping, bulk packaging, the environment, cleaning solvents etc. Since metal residues do not provide any therapeutic benefit to the patient, and product risk should commensurate with the level of product benefit, the specification of a pharmaceutical substance or the drug product may need to include a limit and validated method for metal residues to guarantee acceptable product quality. The considerations for such a requirement should be made in a manner that is consistent with safety- and quality-based criteria as well as GMP, GDP and any other relevant provisions.

The objective of this guideline is to recommend maximum acceptable concentration limits of metal residues arising from the use of metal catalysts or metal reagents in the synthesis of drug substances and excipients. Since the use of these metals is restricted to defined chemical reactions, limitation of their residues in pharmaceutical substances themselves will normally be sufficient. Thus, limitation of these metal residues in the final drug product will normally not be necessary. The concentration limits in this guideline are based on safety criteria and assure an adequate quality of the pharmaceutical substance and the drug product. It is therefore not considered appropriate to expect that the pharmaceutical industry tightens the concentration limits in the regulatory dossier on basis of GMP, process capabilities, or any other quality criteria.

Since the origin of metal residues is irrelevant regarding their potential toxic effects, the concentration limits in this guideline are in principle also applicable to residues from other sources than catalysts and reagents. However, for these other sources adoption of a concentration limit and a validated method in the specification is only necessary in the very exceptional cases where these residues are known to be insufficiently limited by GMP, GDP or any other relevant provision. Pharmaceutical companies are not supposed to perform extensive tests on metal residue findings of unknown sources to comply with this guideline. They may rely on general information from trustworthy suppliers.

The metals that are currently included in this guideline are listed in Table 1. The guideline may be updated to include other metal residues in due course. Any interested party can make a request and submit the relevant safety data. The classification and concentration limits of the currently included metals may also change when new safety data becomes available.

The following assumptions and/or default values have been used during establishment of the concentration limits:

- Body weight (bw) of an adult: 50 kg.
- Breathing volume of an adult: 20 m^3 per day (24 h).
- Occupational (workplace) inhalation exposure: 8 h per day (24 h).
- Exposure limits were established using uncertainty factors as described in appendix 3 of the ICH Q3C guidance.
- For pragmatic reasons a number of uncertainty factors were adapted to arrive at a final safe and practical PDE setting - Q3C method for uncertainty factor (UF) calculation plus additional pragmatic factor for PDE calculation.
- Acceptable additional lifetime cancer risk: an increased cancer risk of 1 in 100,000 was identified as acceptable for genotoxic impurities in pharmaceuticals by the CHMP.

2. DEFINITION AND SCOPE

Metal catalysts and metal reagents are defined here as chemical substances that are used to change the rate of chemical reactions or which act on other chemical substances in chemical reactions. For the purpose of this guideline, metal catalysts and metal reagents refer to metals used in the synthesis of the active pharmaceutical ingredient, the synthesis of any of the pharmaceutical excipients, or the synthesis of any of the pharmaceutical excipients used during the manufacture of the drug product but no longer present in the drug product itself. Metal residues can either be present in the original form of the metal or as a form of the metallic element altered by downstream chemical processing.

This guideline applies to new and existing marketed drug products. However, for existing marketed drug products a time limit of 5 years is set for the implementation of the guideline in case an earlier implementation is not feasible. Following this 5 years implementation, transitional period only drug products which have been manufactured using pharmaceutical substances which comply with the guideline can be released to the market. This guideline does not apply to potential new drug substances or to excipients used during the clinical research stages of development of a medicinal product. During the clinical research stages of development, higher limits of metal residues might be acceptable.

The guideline does also not apply to metals that are deliberate components of the pharmaceutical substance (such as a counter ion of a salt) or metals that are used as a pharmaceutical excipient in the drug product (e.g. an iron oxide pigment). As described in the introduction, the guideline does normally not apply to extraneous metal contaminants that are more appropriately addressed by GMP, GDP or any other relevant quality provision.

The route of administration may influence the actual exposure of the human body to the metal. Due to the limited oral bioavailability of many metals, this guideline applies different limits to oral and parenteral routes of administration. As other routes of exposure may have different toxicological implications, specific limits have also been set for the inhalation exposure to some metals. When the exposure is short, the PDEs mentioned in this guideline may be adapted as indicated in section 4.3.

3. LEGAL BASIS

This guideline should be read in conjunction with Directive 2001/83/EC as amended and in conjunction with all relevant CHMP guidance documents, with special emphasis on:

- Note for Guidance on Impurities in New Drug Products (CPMP/ICH/2738/99, ICHQ3B (R))
- Impurities Testing Guideline: Impurities in New Drug Substances (CPMP/ICH/2737/99, ICHQ3A)
- Note for Guidance on Impurities: Residual Solvents (CPMP/ICH/283/95 in conjunction with CPMP/ICH/1507/02, CPMP/ICH/1940/00 corr, CPMP/QWP/450/03 and CPMP/QWP/8567/99)

- Guideline on the Limits of Genotoxic Impurities (EMEA/CHMP/QWP/251344/2006 and CPMP/SWP/5199/02)

- Validation of Analytical Procedures: Text and Methodology (CHMP/ICH/381/95, ICHQ2(R1))

4. MAIN GUIDELINE TEXT

4.1 Classification

The term tolerable daily intake (TDI) is used by the International Program on Chemical Safety (IPCS) to describe exposure limits of toxic chemicals, whereas the term acceptable daily intake (ADI) is used by the World Health Organization (WHO) and other national and international health authorities and institutes. Following the ICH Q3C guideline on residual solvents, a 'new' term was chosen to avoid confusion of terms and their meaning. As for the ICH Q3C guideline, the new term is called the Permitted Daily Exposure (PDE). For the purpose of this guideline, the PDE is defined as the pharmaceutically maximum acceptable exposure to a metal on a chronic basis that is unlikely to produce any adverse health effect.

Metal residues should be evaluated for their potential risk to human health and placed into one of the following three classes:

Class 1 Metals: Metals of significant safety concern. This group includes metals that are known or suspect human carcinogens, or possible causative agents of other significant toxicity.

Class 2 metals: Metals of low safety concern. This group includes metals with lower toxic potential to man. They are generally well tolerated up to exposures that are typically encountered with administration of medicinal products. They may be trace metals required for nutritional purposes or they are often present in food stuffs or readily available nutritional supplements.

Class 3 metals: Metals of minimal safety concern. This group includes metals with no significant toxicity. Their safety profile is well established. They are generally well tolerated up to doses that are well beyond doses typically encountered with the administration of medicinal products. Typically they are ubiquitous in the environment or the plant and animal kingdoms.

4.2 Exposure Limits

A general set of safety based limits is defined for residues of each particular class of metals, taking into account the route of administration.

Table 1 provides information on acceptable PDEs and concentration limits for residues of the currently included fourteen metals following oral, parenteral and/or inhalation exposure. The metals that are currently included in Class 1 are further subdivided into three subclasses called class 1A, 1B and 1C. The exposure limits in class 1A (platinoids) and 1C relate to the individual metals, whereas the exposure limits in class 1B (also platinoids) relate to the total amount of the listed metals. For the platinoid metals in class 1B, a conservative approach was adopted because the currently available toxicity data is rather limited. Therefore the indicated limit for Class 1B is the limit for the total amount of these platinoid metals that, based on the used synthesis procedures, is anticipated to be present.

Table 1: Class Exposure and Concentration Limits for Individual Metal Catalysts and Metal Reagents

Classification	Oral Exposure		Parenteral Exposure		Inhalation exposure *
	PDE (µg/day)	Concentration (ppm)	PDE (µg/day)	Concentration (ppm)	PDE (ng/day)
Class 1A: **Pt, Pd**	100	10	10	1	Pt: 70 *
Class 1B: **Ir, Rh, Ru, Os**	100**	10**	10**	1**	
Class 1C: **Mo, Ni, Cr, V** Metals of significant safety concern	250	25	25	2.5	Ni: 100 Cr (VI): 10
Class 2: **Cu, Mn** Metals with low safety concern	2500	250	250	25	
Class 3: **Fe, Zn** Metals with minimal safety concern	13000	1300	1300	130	

** see section 4.4 and the respective monographs, Pt as hexachloroplatinic acid*

*** Subclass limit: the total amount of listed metals should not exceed the indicated limit*

4.3 Setting Concentration Limits Metal Residues

4.3.1 General

If synthetic processes of pharmaceutical substances are known or suspected to lead to the presence of metal residues due to the use of a specific metal catalyst or metal reagent, a concentration limit and validated test for residues of each specific metal should be set. All concentration limits should be realistic in relation to analytical precision, manufacturing capability, and reasonable variation in the manufacturing process. Since the use of metal catalysts or metal reagents during synthesis is restricted to defined chemical reactions, limitation of their residues in pharmaceutical substances itself will normally be sufficient. A limit for a metal residue in the pharmaceutical substance may however be replaced by a limit for that metal residue in the final medicinal product, as described below.

4.3.2 Pharmaceutical products applied via the oral, parenteral or inhalation route of administration.

Two options are available when setting a concentration limit for a metal residue.

Option 1: For each metal, the concentration limit in parts per million (ppm) as stated in Table 1 can be used. The concentration limits in Table 1 have been calculated using equation (1) below by assuming a daily dose of 10 grams of the drug product.

$$(1) \quad Concentration\,(ppm) = \frac{PDE\,(\mu g / day)}{daily\,dose\,(g / day)}$$

If all pharmaceutical substances in a drug product meet the option 1 concentration limit for all metals potentially present, then all these substances may be used in any proportion in the drug product as long as the daily dose of the drug product does not exceed 10 grams per day. When the daily dose of the drug product is greater than 10 grams per day, Option 2 should be applied.

Option 2a: The PDE in terms of µg/day as stated in Table 1 can be used together with the actual daily dose of a pharmaceutical substance in the drug product to calculate the concentration of residual metal allowed in that pharmaceutical substance.

Option 2b: Alternatively, it is not considered necessary for each pharmaceutical substance to comply with the limits given in Option 1 or the calculated limits using Option 2a.

The PDE in terms of µg/day as stated in Table 1 can also be used with the known maximum daily dose of the drug product to determine the concentration of a metal residue originating from any of the pharmaceutical substances in the drug product (not the substance). This approach is considered acceptable provided that it has been demonstrated that the metal residue has been reduced to the practical minimum in every substance. This approach implies that the maximum levels of a metal in certain substances may be higher than the option 1 or option 2a limit, but that this should then be compensated by lower maximum levels in the other substances.

4.3.3 Pharmaceutical products applied via other routes of administration

The concentration limits should be set in consideration of the route of administration.

Without proper justification, parenteral limits/PDEs should be used for pharmaceutical substances that are administered by other routes of administration, including inhalation. Oral limits/PDEs may be applied if the absorption by other routes of administration is not likely to exceed the absorption following oral administration. For example, for cutaneous administration, oral concentration limits/ PDEs are considered acceptable.

Platinum salts have been shown to be allergenic, with hexachloroplatinic acid being clearly the most allergenic (Malo, J-L, 2005). Consequently a specific limit for inhalation exposure for this molecule has been set at 70 ng/day (see monograph). Chromium VI and Nickel, when inhaled, have been associated with carcinogenicity. Therefore specific limits for inhalation exposure have been set for Chromium VI at 10 ng/day and for Nickel at 100 ng/day (see respective monographs).

4.3.4 Pharmaceutical products used for short-term and for life-saving indications

As the PDEs and concentration limits mentioned in this guideline are based on chronic use, higher PDE's and concentration limits may be acceptable in cases of short-term use (30 days or less). For instance, this may be applicable to contrasting agents, antidotes, or products for diagnostic use. This may however only be applied if neither an Option 1 nor an Option 2 limit is feasible.

Specific risk-benefit considerations, such as for compounds used for life-saving indications, may also warrant the use of higher limits. Justifications should be made on a case-by-case basis.

4.4 Analytical Procedures

For the determination of each metal residue an appropriate and validated method should be used. Attention should be paid to the fact that metal residues may be present in a different form than the form of the element in the original catalyst or reagent. Unless otherwise justified, the test should be specific for each element. Where sufficient justification can be derived, a more general analytical method encompassing one or more metal residues with a general concentration limit can be appropriate if it can be shown that the exposure limit for none of the specified metals would be exceeded.

Any harmonized procedures for determining levels of metallic residues as described in the pharmacopoeias should be used, if feasible. Otherwise, manufacturers are free to select the most appropriate validated analytical procedure for a particular application. If only residuals of Class 2 or Class 3 metals are present, a non-specific method may be used. Specifically with respect to platinoid

Class 1B, where a group limits applies, it is accepted that due to technical limitations, the lower limit of detection may not be below 0.5 ppm for individual platinoids.

General semi-quantitative metal limit tests based on the precipitation at pH 3.5 of coloured metal sulfides are described in several publications (e.g. Ph. Eur.). Such tests are not suitable to quantitatively determine the actual levels of a specific metal residue in a pharmaceutical substance. If adjusted (e.g. by using standard addition methods) and properly validated (including cross-validation with an element-specific test), a test based on the principle of sulfide precipitation, may be suitable for routine testing in some cases.

4.5 Batch Results, Testing Frequency and Deleting of a Test from the Specification

If synthetic processes are known or suspected to lead to the presence of metal residues due to the use of a specific metal catalyst or metal reagent, element specific assays should be undertaken to determine the actual amount of these metal residues, particularly during the development of the synthetic process.

If the synthetic or manufacturing processes have shown to result in the removal of a potential metal residue, routine testing of that metal residue may be replaced by non-routine (skip) testing. A metal residue can be considered adequately removed if, in 6 consecutive pilot scale batches or 3 consecutive industrial scale batches less than 30 % of the appropriate concentration limit was found. A change from routine to non-routine testing does not mean that the test may also be deleted from the specification.

Only for class 3 metals, the test may be deleted from the relevant specification if the drug product manufacturer sufficiently demonstrates that the adequate removal of the metal residue from the pharmaceutical substance or the drug product is guaranteed.

4.6 Reporting Levels of Metallic residues

Manufacturers of medicinal products need information about the content of metallic residues in pharmaceutical substances in order to meet the criteria of this guideline. Thus, it is necessary that the manufacturers of pharmaceutical substances provide a clear statement on the identity and quantity of all metal residues present in their compounds to the drug product manufacturers. The following statements are given as acceptable examples of such information.

- Only Class 3 metals are likely to be present. All are below the Option 1 limit for <oral> or <parenteral> exposure (here the supplier would define the applicability, either oral or parenteral product).
- Only Class 2 metals X, Y, . . . are likely to be present. All are below the Option 1 limit for <oral> or <parenteral> exposure (here the supplier would name the Class 2 metals represented by X, Y, ... and define the applicability, oral or parenteral of the product).
- Class 1 metal Z is likely to be present. The metal is present in a concentration of zzz ppm which is below <the acceptance criterion> (here the supplier would state the identity of the metal, the actual concentration found and the applied acceptance criterion. If the metal is found below the LOD or LOQ of the applied analytical method, than the LOD and LOQ of this method are given).

"Likely to be present" refers to the metal used in the final manufacturing step and to metals that are used in earlier manufacturing steps and not removed consistently by the manufacturing process.

5. GLOSSARY

ACGIH	American Conference of Governmental Industrial Hygienists
ADI	Acceptable daily intake
ATSDR	Agency for Toxic Substances and Disease Registry
Body weight of an adult	The weight adjustment assumes an arbitrary adult human body weight for either sex of 50 kg. This relatively low weight provides an additional safety factor against the standard weights of 60 kg or 70kg that are often used as well.
bw	Body weight of an adult
Daily dose	Maximum daily dose related to the product mass of a pharmaceutical substance or a drug product
ESADDI	Estimated safe and adequate daily intake
FSA	Food Standard Agency
GDP	Good Distribution Practice for medicinal products for human use
GMP	Good Manufacturing Practice
IPCS	International Program on Chemical Safety
LOEL	Lowest observed effect level
LOD	Limit of Detection
LOQ	Limit of Quantification
MDD	Maximum daily dose
NOEL	No-observed effect level
PDE	Permitted daily exposure
Pharmaceutical substance	A substance in the drug product (normally an active pharmaceutical ingredient or an excipient)
PMTDI	Provisional maximum tolerable daily intake
ppm	Parts per million
RfD	Reference Dose
TDI	Tolerable daily intake
TTC	Threshold of toxicological concern
UF	Uncertainty factor
US EPA	United States Environmental Protection Agency

6. REFERENCES (scientific and / or legal)

- Directive 2001/83/EC (as amended) by Directive 2004/24/EC
- Guideline on the Limits of Genotoxic Impurities (CPMP/SWP/5199/02)
- Impurities Testing Guideline: Impurities in New Drug Substances (CPMP/ICH/2737/99, ICHQ3A)
- Maintenance Note for Guidance on Impurities: Residual Solvents (CPMP/ICH/1507/02, ICHQ3C (M))
- Malo, J-L. Occupational rhinitis and asthma due to metal salts. Allergy 60: 138-139, 2005
- Note for Guidance on Impurities in New Drug Products (CPMP/ICH/2738/99, ICHQ3B (R))
- Note for Guidance on Impurities: Residual Solvents (CPMP/ICH/283/95, ICHQ3C)
- Note for Guidance on Validation of Analytical Methods: Definitions and Terminology (CPMP/ICH/381/95, ICHQ2A)
- Note for Guidance on Validation of Analytical Procedures: Methodology (CPMP/ICH/281/95, ICHQ2B)
- Uter et al., Contact Dermatitis, 1995, 32, 135-142
- Validation of Analytical Procedures: Text and Methodology (CHMP/ICH/381/95, ICHQ2(R1))

APPENDIX 1: RATIONALE FOR PDE SETTING

A variety of metals, mostly transition elements, are employed as such and/or as complexes or salts in organic chemical synthesis to act as catalysts particularly for reactions (e.g., alkene hydrogenation) or as reagents. Any pharmaceutical active substance (or excipient) whose synthesis involves the use of one or more metal catalysts or reagents thus may contain residual metal(s) in the form of the original catalyst(s) or as derivatives produced by downstream chemical processing.

There are a number of problematic aspects associated with providing recommendations on safe limits for metal residues in pharmaceuticals, the main ones being:

Speciation and Form: Transition elements have the potential to form numerous molecular species mainly dependent on oxidation state, co-ordinating ligands and solvation. This property leads to uncertainty over the likely form of metal catalyst residues in biological systems. In addition, toxicity can vary greatly depending on the aqueous solubility of the particular metal salt employed for toxicological evaluation.

Balance of nutritional and toxic effects: Although all metals have inherent toxic properties, some elements such as Fe, Zn, Cr, Mn, Cu and Mo (and possibly V) are important in human nutrition.

Route of administration: Many metals are poorly absorbed from the gastrointestinal tract and so are likely to show differential toxicity between oral and parenteral routes of administration. *Administration by the inhalation route may also lead to different toxicity profile.*

Duration of/age at exposure: Some elements (e.g., Pb, Cd) are cumulative toxins while others, particularly the essential elements, are excreted efficiently. Infants and young children may be particularly sensitive to toxic effects of metals because they tend to absorb a higher fraction of an oral dose, and developing body systems (particularly the nervous system) may be more sensitive than mature systems. Fortunately, on the basis of the available data none of the elements under consideration appears to have a significant propensity to accumulation following oral administration. Infants and young children are likely to receive proportionately lower doses of pharmaceutical products and, although the proposed limits apply principally to adults, they have been set at a sufficiently low level to be applicable to younger age groups.

Data availability: Toxicological (animal and/or human) information on most metals is restricted to a limited number of test types using just the oral route and is available on only a few representative compounds. Except for Pt the toxicological database on the platinum group metals, which appear to have broadly similar chemical and biological properties, is extremely limited. Consequently, a single PDE is applied to the platinoid elements.

Genotoxicity and carcinogenicity potential: The CHMP has recently adopted the threshold of toxicological concern (TTC) concept for genotoxic impurities. It should however be appreciated that since metals were specific exceptions in applying the TTC concept, metal containing compounds and non-essential metals require a specific assessment to address genotoxic and carcinogenic risks (Kroes et al, 2004). Amongst the Class 1 metals assessed in this guideline, chromium, nickel and platinum are known to have genotoxic or carcinogenic potential at least in a particular form. The details of the PDE determination for the three metals are given in the respective monographs.

Extrapolation of toxicological data: PDEs are derived in general by applying an appropriate "safety" or "uncertainty" factor as in the Q3C guideline to the designated lowest-observed effect level (LOEL) or no-observed effect level (NOEL). Owing to wide variability of the nature, quality and quantity of toxicological data amongst the metal elements of interest, it is not possible to employ a totally consistent approach. Human data and previous published evaluations by regulatory bodies have been utilised wherever possible. As there are very limited non-oral data, as above a single factor (0.1) is used to estimate the parenteral PDEs compared with oral PDEs.

Interactions: Competition for absorption sites, nutritional status and other factors can lead to interactions amongst the metal elements, particularly Mo, Zn, Fe and Cu. However, this is unlikely to be a major issue in the case of metal catalyst residues given their anticipated minor contribution to metal intakes.

APPENDIX 2: MONOGRAPHS ON ELEMENTS

PLATINUM (Pt)

Introduction

Pt is a Group VIII element of the third transition series. It is the most important of the six heaviest of the group VIII elements, collectively called the "platinum group metals" or "platinoids".

Pt and Pd are more chemically reactive than the other platinoids. Metallic Pt has been shown to catalyse many oxidation-reduction and decomposition reactions and the major industrial use of Pt is as a catalyst. It is increasingly used as an automobile exhaust gas catalyst and is also used in jewellery and dentistry,

Pt complexes exhibiting a range of oxidation states are known, although the principal valences are Pt II and IV. Pt II forms a tetra-coordinate aqua ion $[Pt(H_2O)_4]^{2+}$. A variety of amine complexes such as the anti-tumour compound *cis*-$PtCl_2(NH_3)_2$ (*cis*-platin) are also known. The most important Pt IV compounds are salts of the red hexachloroplatinate ion $PtCl_6^{2-}$.

Dietary Intake

Mean UK dietary intake 0.2 µg/day; 97.5 percentile intake 0.3 µg/day (Ysart *et al*, 1999).

Toxicological Data

Gastrointestinal absorption of Pt salts is extremely low (<5% of oral dose). Excretion of most of the absorbed fraction is normally via the faeces.

The acute toxicity of Pt salts is dependent on water solubility (the more soluble salts being more toxic) and speciation. A range of Pt IV salts are reported to have rodent oral LD_{50} values from 10 to >1100 mg/kg.

Repeated-dose toxicity studies have been undertaken in the rat using Pt salts in the drinking water for periods of up to 30 days. Only $PtCl_4$ and $Pt(SO_4)_2 \times 4H_2O$ produced initial transient effects on growth rate. The NOEL for administration of $PtCl_4$ for 30 days is 13 mg Pt/kg/day.

Some soluble platinum salts have been reported to be mutagenic *in vitro*.

Cis-platin and carboplatin, widely employed in cancer chemotherapy, are thought to act mainly by adduct formation with both nuclear and mitochondrial DNA. As well as being generally cytotoxic, they exhibit a range of other animal and human toxicities. In animals and/or humans *cis*-platin has been reported to show myelotoxicity, nephrotoxicity and ototoxicity. In clinical use a variety of dosing regimens are used for *cis*-platin, employing for example daily administration for 5 days at *ca* 0.25 mg Pt/kg/day *iv*, possibly with additional doses at weekly or 2-weekly intervals. The human 13-day LOEL in terms of toxicity is reported as 0.3 mg Pt/kg *iv* (Lewis, 1996).

For cisplatin there is sufficient evidence for carcinogenic effects on animals, no experimental data are available for the carcinogenicity of platinum and platinum compounds. However, cisplatin and its analogues are rather exceptional by comparison with other platinum compounds. This is reflected in the unique mechanism for their anti-tumour activity. Intrastrand DNA cross-links, formed only by the cis isomer at a certain position of guanine, are regarded as reasons for this anti-tumour activity. It appears that replication of DNA in cancer cells is impaired; while in normal cells the cisplatin lesions on guanine are repaired before replication.

Occupational exposure to platinum compounds, particularly those containing reactive chlorine, is associated with respiratory symptoms and skin reactions.

In 2000, Merget and co-workers (Merget et al. 2000) derived a NOEL of 1.5 ng soluble Pt per m^3 for allergy due to occupational exposure to airborne soluble Pt-salts. This NOEL was taken from a 5 year epidemiological study as the approximate upper quartile of occupational exposure levels at which no new sensitisations occurred. The dose-effect relationship seems to be rather steep: at occupational levels of 14 - 37 ng/m^3 (medians of area sampling) 13 new sensitisations were seen (115 subjects, 5 years exposed). Hence, as suggested by the authors, an occupational level of 10 ng/m^3 may be considered as safe. This value corresponds to 70 ng/day (based on a daily breathing volume of 20 m^3 and 8 h exposure).

Cristaudo and co-workers confirmed that platinum salts are a cause of sensitisation (Cristaudo et al. 2005). The reason for the increased allergic properties of haxachloroplatinic acid when compared to other platinum salts and other metal salts of the second and third group elements is thought to be related to the molecular structure of the compound.

Regulatory Assessment

No regulatory assessments appear to be available for Pt. The American Conference of Governmental Industrial Hygienists (ACGIH®) has adopted a Threshold Limit Value (TLV) of 1 mg/m^3 for platinum metal and 0.002 mg/m^3 for soluble salts to protect against sensitisation. The later is equivalent to a daily exposure of 40 µg/day (20 m^3 air/day, EPA value).

Pt and its compounds have a wide spectrum of toxicity ranging from a relatively low toxicity of Pt metal to genotoxic/cytotoxic effects (e.g. *cis*-platin) and sensitisation reactions associated with some Pt salts and complexes. Consequently, a conservative approach to the assessment of an appropriate PDE has been adopted.

Conclusion

Oral PDE: rat NOEL of 13 mg Pt/kg/day for PtCl4 and safety factor of 5,000 (5 × 10 × 10 × 10 × 1) yields a PDE of 2.6 µg Pt/kg/day, equivalent to 130 µg/day for a 50 kg person. For practical reasons this value is rounded to an oral PDE of 100 µg/day.

Parenteral PDE: human iv 13-day LOEL for cis-platin of 300 µg Pt/kg is equivalent to ca 25 µg Pt/kg/day. Applying a safety factor of 100 (human data but LOEL not NOEL) yields a PDE of 0.25 µg Pt/kg/day. For practical reasons this value is rounded to a parenteral PDE of 0.2 µg Pt/kg/day. For a 50 kg person 10 µg Pt/day.

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PALLADIUM (Pd)

Introduction

Palladium is a metallic element, which resembles and occurs together with the other platinum group metals and nickel. It is present at very low concentrations (<1 µg/kg) in the earth's crust [1]. Palladium alloys are widely used in dentistry (e.g., for crowns and bridges), thus representing the most frequent cause of constant palladium exposure.

Diet intake

Palladium levels detected in food ranged from 0.3 (milk and poultry) to 15µg/kg fresh weight (honey sample collected from a polluted area). In general the amounts of palladium exceeded those of platinum found in diverse food groups. The human average dietary intake of palladium appears to be up to 2 µg/day.

Toxicological Data

Palladium ions are poorly absorbed from the digestive tract (< 0.5 % of the initial dose in adult rats). After intravenous administration the highest concentration of palladium was found in kidney, liver, spleen, lymph nodes, adrenal gland, lung and bone. Transfer of small amounts of palladium to offspring has been demonstrated.

Palladium ions were found to be eliminated in faeces and urine. Urinary excretion rates of intravenously dosed rats and rabbits ranged from 6.4 to 76 %. Following oral administration > 95 % of palladium was eliminated in faeces of rats due to non-absorption.

Acute toxicity

LD_{50} values for palladium compounds ranges, depending on compound and route of administration, from 3 to 4900 mg/kg body weight, the most toxic being $PdCl_2$, the least toxic PdO_2. With regard to routes of exposure of palladium compounds, oral administration was associated with the lowest degree of toxicity, due to poor absorption.

Short-term exposure

A 28-day oral toxicity study in rats with tetraammine palladium hydrogen carbonate at dose levels of 1.5, 15 and 150 mg/kg body weight per day produced treatment-related changes mainly at the 2 higher concentrations. In this study the no-observed-adverse-effect level (NOAEL) was considered to 1.5 mg/kg body weight per day. With regard to intravenously administered palladium compounds no NOAEL has been established in the studies available.

Long-term exposure

Mice given $PdCl_2$ in drinking water (5 mg palladium/l) for a lifetime showed suppression of body weight and an increase in amyloidosis of several inner organs. In another study of questionable value (chloropalladosamine was given enterally to rats for about 6 months) a dose of 0.08 mg/kg body weight (corresponding to 0.041 mg Pd^{2+}/kg) was determined as the no-observed-effect-level (NOEL), above which changes in body weight, hemoglobin content, blood serum parameters as well as functional and morphological changes have been reported. There is insufficient histological information available from this study.

Irritation and sensitization

Palladium compounds have been shown to cause eye irritation and some have been found to be potent sensitizers of the skin

Reproductive and developmental toxicity

There are insufficient data on the reproductive and developmental effects of palladium and its salts.

Genotoxicity

With the exception of a chromosome aberration test in human lymphocytes, mutagenicity tests of several palladium compounds with bacterial or mammalian cells *in vitro* (i.e. Ames test, SOS chromotest in E. coli, micronucleus test in human lymphocytes) gave negative results. An *in vivo* micronucleus test in the mouse performed with tetra ammine palladium hydrogen carbonate yielded negative results at doses ranging from 125 mg to 500 mg/kg body weight.

Palladium compounds may interact with isolated DNA *in vitro*. The interaction with nucleic acids seems to be of non-covalent nature (hydrogen bond).

Carcinogenicity

Mice (white, Swiss Charles River CD) given palladium(II) chloride at 5 mg Pd^{2+}/litre in drinking-water (corresponding to about 1.2 mg Pd^{2+}/kg body weight per day by assuming a body weight of 0.03 kg and a daily water uptake of 7 ml) over a lifetime (from weaning to natural death) developed tumors in both sexes (19/65 [29%] versus 13/80 [16%] in control; sex-related distribution not specified). Only one tumor found in the exposed group was not malignant. Most of the malignant tumors were either lymphoma-leukemia types (10 versus 2 in controls) or adenocarcinoma of the lung (6 versus 1 in controls). The increase in malignant tumors (18/65 [27.7%] versus 11/80 [13.8%]) was statistically significant ($P < 0.05$) compared with the simultaneous control group. This was not the case in comparison with another smaller, non-simultaneous control group, which had differing rates of malignant (6/41 [14.6%]) and total (11/41 [26.8%]) tumors (Schroeder & Mitchener, 1971). The increased tumor rate might be caused by a significantly enhanced longevity (mean age of the last 10% of surviving males: 815 ± 27 versus 696 ± 19 days in controls). Other limitations of this study refer to dosage regimen (only one dose was tested) and protocol (tumor rates were pooled for males and females).

Effects on humans

Most of the case reports refer to palladium sensitivity associated with exposure to palladium-containing dental restorations, symptoms being contact dermatitis, stomatitis or mucositis. Side–effects noted from other medical or experimental uses of palladium preparations include fever, haemolysis, discoloration or necrosis at injection sites after subcutaneous injections and erythema and oedema following topical application.

Subpopulations at special risk of palladium allergy include people with known nickel allergy.

Regulatory Assessment

In Germany, the maximum recommended workplace level (MAK: Maximale Arbeitsplatz-konzentration) for poorly soluble compounds (metals and their oxides) is 0.1 mg/m^3, while for aerosols of all soluble compounds of platinum and platinoids a maximum level of 0.001 mg/m^3 is recommended, equivalent to a daily exposure value of 1µg × $20m^3$ × (8/24) × (5/7) rounded to 5 µg/day.

Conclusion

Overall, the available data are limited, including the database on reliable long-term studies in animals, precluding an adequate assessment of the effects of chronic enteral or parenteral exposure to Pd.

However, for pragmatic reasons, an oral PDE for palladium is set at 100 µg/day (2 µg/kg/day in a 50 kg person) based on a mice NOEL/LOEL of 1.2 mg/kg/day and an uncertainty factor of 12 × 10 × 1 × 5 × 1 = 600 (per Q3C method). A parenteral PDE is set at 10 µg/day, assuming a 10% bioavailability.

IRIDIUM (Ir)

Introduction

Ir is a Group VIII platinoid element of the third transition series. The chemistry of Ir and its complexes is quite similar to that of Rh. Ir exhibits four main oxidation states I-IV, though only Ir II and Ir IV appear to be relevant to aqueous environments.

Dietary Intake

Mean UK intake: 2 µg/day; 97.5 percentile intake 3 µg/day (Ysart *et al*, 1999).

Toxicological Data

There are very few published animal data, and those available are of uncertain reliability.

Very limited data have been reported from studies in humans.

Conclusion

Insufficient toxicological data are available on which to base a reliable assessment.

RHODIUM (Rh)

Introduction

Rh is a platinum group VIII element of the second transition series. Its principal oxidation states are I, II and III, though Rh III is the most common state, especially in terms of aqua ion formation. Rh catalysts (Rh-Pt metal alloy; Rh CO complexes) are widely used.

Dietary Intake

Mean UK intake: 0.2 µg/day; 97.5 percentile intake 0.4 µg/day (Ysart *et al*, 1999).

Toxicological Data

Oral uptake is reported to be very low.

Single-dose rat toxicity data on $RhCl_3$ indicate that the *iv*/oral LD_{50} values are *ca* 200 and > 500 mg/kg respectively.

Simple Rh compounds such as $RhCl_3$ have been reported as genotoxic, e.g. in *Salmonella typhimurium* TA98, and others as cytotoxic. No repeated-dose toxicity data were located.

Conclusion

Insufficient animal/human toxicity data are available for risk evaluation purposes. Rh compounds appear to be less toxic than their Pt counterparts.

RUTHENIUM (Ru)

Introduction

Ru is a platinum group metal of the second transition series. It exhibits a wide range of oxidation states, the most common being II, III and IV.

Ruthenium tetraoxide, RuO_4, is a more volatile and vigorous oxidant than OsO_4.

$Ru(OH)_2$, $RuCl_4$ and RuO_2 are stable and water soluble; generally Ru III salts are insoluble in water. Ru is employed as a hardener in Pt/Ru alloys which are used in electrical contacts.

Dietary Intake

Mean UK intake: 4 µg/day; 97.5 percentile intake, 6 µg/day (Ysart *etal*, 1999).

Toxicological Data

Oral absorption of Ru is low (up to 3.5% in rodents).

Oral and intraperitoneal (ip) LD_{50} values have been determined in rodent species for several Ru compounds:

Compound	Oral LD_{50} (mg/kg)	*ip* LD_{50} (mg/kg)	Species
Ru chloride hydroxide ($Ru(OH)Cl_3$)	463	225	Mouse
Ru oxide (RuO_2)	5570	3050	Mouse
Ru oxide (RuO_2)	4580	-	Rat

Several Ru complexes with potential medical application have been reported to cause genotoxic responses *in vitro* (e.g. in *Salmonella typhimurium* strains TA98 and TA100), although the magnitude of the effects was much less than in the case of *cis*-platin.

No data from repeated-dose toxicity studies could be located.

Conclusion

Based on data from acute toxicity studies on simple Ru compounds, and on the genetic toxicity of some complexes containing nitrogenous ligands, Ru compounds/complexes appear likely to be less

toxic than their Pt counterparts. However, insufficient data are available on which to base a reliable assessment.

OSMIUM (Os)

Introduction

Os is one of the six platinum group metals, the six heaviest elements in Group VIII. Os belongs to the third transition series. Os complexes exhibit a wide range of oxidation states, the most common being Os III, IV and VI.

Osmium tetraoxide (OsO_4) is a volatile, toxic and powerful oxidant used in chemical synthesis and in dilute aqueous solution as a biological stain for adipose tissue, being readily reduced by organic matter to a black oxide. OsO_4 is a severe irritant of the eyes and respiratory tract.

There are strong analogies between Os and Ru in terms of chemical reactivity.

Dietary Intake

No information on dietary intake could be found. However, given the rare occurrence of Os, human dietary intakes are expected to be extremely low (< 1 μg/day) except perhaps in areas close to metal smelters.

Toxicological Data

No data appear to be available apart from several reports on the effects of OsO_4 on synovial membranes in connection with the use of 1% OsO_4 solutions for chemical synovectomy of arthritic joints. Most of the injected Os is excreted in urine with no evidence for accumulation in the contralateral knee, the regional lymph nodes, the liver or the heart.

Conclusion

Insufficient toxicological data are available on which to base a reliable assessment.

MOLYBDENUM (Mo)

Introduction

Mo is a Group VIB element of the second transition series. Its main oxidation states are IV and VI, 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+}. MoO_2 and MoS_2 are insoluble in water. Mo metalloenzymes have a vital role in plants and bacteria particularly in respect of nitrate reductase and nitrogenase. In man, Mo-containing xanthine oxidase catalyses the oxidation of hypoxanthine and xanthine as part of the degradation pathway of purine nucleic acids to uric acid. Mo deficiency, characterised by night blindness, nausea, disorientation and coma and associated with various biochemical abnormalities including high plasma methionine and almost undetectable serum uric acid, has been reported in a patient receiving total parenteral nutrition.

Dietary Intake

Mean UK intake 0.12 mg/day; 97.5 percentile intake 0.21 mg/day (Ysart *et al* 1999). The US ESADDI is based on the current US dietary intake of 75-250 µg/day. A maximum level in drinking water of 0.07 mg/l has been recommended by WHO. Intakes of 10-15 mg/day may be associated with altered nucleotide metabolism and impaired Cu bioavailability. A safe intake for UK adults of 50-400 µg/day has been recommended (Department of Health, 1991). WHO has estimated a daily adult Mo requirement of 100-300 µg.

According to WHO (1996) the daily requirement is 0.015 to 0.15 mg per day for children and 0.075 to 0.25 mg per day for adults, i.e. about 1-5 µg/kg/day.

Toxicological Data

Gastro intestinal absorption depends on the chemical form. Absorption of Mo VI from the gastrointestinal tract is reported to be good for soluble compounds (40-85% in the rat; 85-93% in man). Absorption and retention of Mo is markedly influenced by interactions with dietary Cu and sulphate. Cu forms insoluble copper thiomolybdate in the digestive tract and high dietary inorganic sulphate is believed to reduce intestinal absorption by blocking the transport of Mo through the cell membrane.

The acute toxicity of Mo compounds is related to their solubility. MoO_3, $CaMoO_4$ and $(NH_4)_2$ MoO_4 caused fatalities in rats at oral doses of 1.2-6.0 g Mo/kg, whereas insoluble MoS_2 was essentially non toxic at up to 6.0 g Mo/kg.

The chronic toxicity of Mo has not been extensively studied in laboratory animals. Virtually all of the published studies date back to the 1940s-1970s and focus on Mo toxicity in cattle and other livestock that seem to lack tolerance for Mo. In a 5/7–week dietary study in the rabbit with Na_2MoO_4, the NOEL is estimated as 7 mg/kg/day.

There is little information on the genotoxicity of molybdenum. Evidence for the genotoxic potential of sodium and ammonium molybdate has been reported in vitro in human and mice assays and in vivo in mice. Other compounds such as molybdenum trioxide, or molybdenum chloride were negative in mutagenic or recombinogenic in vitro assays. RIVM assessment was that the available data suggest that molybdenum is not a genotoxic compound (RIVM report 711701025)

NTP conducted a 2 year carcinogenicity study of molybdenum trioxide administered by inhalation in rats and mice. It was concluded that while that rat study was negative, there was a slightly increased incidence of alveolar/bronchiolar adenomas or carcinomas (combined) in male and female mice at 100 mg/m3. The NOAEL was set at 10 mg/m^3 for chronic inflammation.

Regulatory Assessment

RIVM: oral Tolerable Daily Intake (TDI) of 10 µg/kg/day. Tolerable Concentration in Air (TCA) 12 µg/m^3

This is equivalent to 240 µg/day (Using 20 m^3 air/day inhaled per EPA).

WHO drinking quality guideline is 70 µg/L, based on a NOAEL for human exposed to molybdenum in drinking water of 0.2 mg/L in Denver (Colorado) and an uncertainty factor of 3 for intra-human variation.

ACGIH set a TLV-TWA (threshold limit value time weighted average) at 0.5 mg/m^3 for soluble compounds and higher values for metallic molybdenum and insoluble compounds. This is equivalent to 1.45 mg/day (0.5/1000 × 0.5l × 12 × 60 × 8).

US EPA. Oral RfD for Mo = 5 µg/kg/day, based on an increase in urinary uric acid in humans exposed to 10 mg Mo/day in the diet based on an epidemiological study in the Soviet Union (1961),

using an uncertainty factor of 10 for the LOAEL and a factor of 3 for the protection of sensitive humans (IRIS, revision 1993).

Conclusion

Oral PDE: 300 µg Mo/day (following RIVM approach – TDI of 10 µg Mo /kg/day; body weight of 50 kg and safety factor of 0.6). Estimated parenteral PDE: 30 µg Mo/day (based on an oral bioavailability of 50% and on the TCA determined by RIVM with an uncertainty factor of 8).

NICKEL (Ni)

Introduction

Ni is a Group VIIIB element of the first transition series. Although it can exhibit valences of 0, I, II and III, its main oxidation state is +2.

Dietary Intake

Mean UK intake: 0.12 mg/day; 97.5 percentile 0.21 mg/day (Ysart et al, 2000). Ni appears to be an essential micronutrient in animals, and so it is likely to be essential for humans, but its precise function in humans is unknown. Estimates of the presumed human Ni requirement range from 5-50 µg/day (Department of Health, 1991).

Toxicological Data

In general, more soluble Ni compounds such as $Ni(NO_3)_2$ are more absorbable than insoluble ones. In the fasted state up to 50% can be absorbed from the gastrointestinal tract, but the extent of absorption can be reduced dramatically in the presence of many food constituents such as ascorbic acid, tannins and phosphates. Thus, most Ni in food remains unabsorbed and ca 10% of Ni with food is absorbed. Ni from drinking water can be up to 25% absorbed, although this is not a major source since Ni levels are normally low.

The rodent LD50 for $NiSO_4$ is reported as ca 300 mg/kg, whereas that for the almost insoluble NiO is >5000 mg/kg.

A number of sub-chronic/chronic toxicity studies on Ni compounds with durations ranging from 3 weeks to 2 years using dietary, oral gavage or drinking water administration have been reported in the literature. A two year rat study (Ambrose et al, 1976) involving dietary administration of $NiSO_4$ over 2 years has been used extensively as a basis for regulatory assessments. The NOEL from this study is 5 mg Ni/kg/day. The same NOEL was obtained from a 90-day rat study on $NiCl_2$ (decreased red blood cell parameters and alterations to serum enzyme activity). A two-year dog study on NiSO4 (Ambrose et al, 1976) revealed lung and bone marrow lesions at the highest dose; the NOEL from this study is assessed as 29 mg Ni/kg/day. Although some in-vitro positive findings in genotoxicity assays (particularly for clastogenicity) have been reported, there is no evidence suggesting that Ni compounds are carcinogenic by the oral route. Chromosome aberrations have been observed in vivo in both humans and laboratory animals following exposure to nickel by inhalation and nickel is carcinogenic by this route. In humans lung and nasal cancer have been associated with inhalation exposure to nickel and/or nickel compounds (RIVM report 711701 025; 2001).

Ni sensitivity and allergic contact dermatitis is well documented, particularly in women (possibly owing to the wearing of Ni-containing earrings in pierced ears). There is evidence suggesting that nickel ingestion may contribute to the exacerbation of eczema in sensitized individuals. It has been documented that oral intakes as low as 0.49 mg but not 0.40 mg could trigger symptoms, particularly

in the fasting state increasing the bioavailability of nickel (Gawkrodger et al, 1986, Nielsen et al, 1990).

Regulatory Assessments

Several bodies have made recommendations on safe levels, generally using a NOEL of 5 mg Ni/kg/day. WHO derived a Tolerable Daily intake of 5 µg/kg/day through use of an uncertainty factor of 1000 (to compensate for the absence of reliable chronic toxicity/carcinogenicity/reproductive toxicity data). EPA set an RfD of 20 µg Ni/kg/day after employing an uncertainty factor of 300.

For inhalation exposure to Nickel, according to Boudet et al (1999) a lifetime exposure of 1.8×10^{-4} µg/m^3 (range: $0.9 \times 10^{-4} - 3.6 \times 10^{-4}$ µg/m^3) nickel was associated with a cancer risk of 8.6×10^{-8} (range: $4.3 \times 10^{-8} - 17.3 \times 10^{-8}$). Based on these data a 1 in 10^5 lifetime risk would be associated with an air concentration of 21 ng/m^3 (range: 5 – 84 ng/m^3).

Conclusion

In consideration of the data on dietary intakes (up to 4.2 µg Ni/kg/day), the use of Ni supplements and the US EPA RfDs, an oral PDE of 300 µg/day (6 µg Ni/kg/day in a 50 kg person) is proposed, based on a NOEL of 5 mg/kg/day and a safety factor of well over 800. This recommended PDE is equivalent to 30% the RfD for Ni proposed by EPA

Estimated parenteral PDE: 30 µg/day (0.6 µg Ni/kg/day in a 50 kg person and based on a bioavailability of 10%)

An inhalation PDE for nickel is set at 100 ng/day. For inhalation exposure, it is relevant to take into account the cancer risk data relating to inhalation exposure of nickel. A lifetime inhalation concentration of 21 ng/m3 (range: 5 – 84 ng/m^3) nickel has been associated with a lifetime risk for cancer of 1 in 10^5, equivalent to 100 ng/day (using the lowest inhalation concentration and 20 m^3 of air/day inhaled). An increased cancer risk of 1 in 100 000 was identified as acceptable for genotoxic impurities in Pharmaceuticals by the CHMP.

CHROMIUM (Cr)

Introduction

Cr is a Group VIII element of the first transition series. A variety of oxidation states are known, but the most important are Cr II, III and VI. Cr II is readily oxidised and is used as a reducing agent in chemical synthesis. Cr VI is a powerful oxidant, chromate, CrO_4^{2-}, and dichromate, $Cr_2O_7^{2-}$, being the best known oxyanions. Cr III, 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). Hexavalent chromium compounds are man-made and do not occur naturally in the environment.

Dietary Intake

Mean UK intake: 0.10 mg/day; 97.5 percentile intake 0.17 mg/day (Ysart *et al*, 2000). An earlier publication (Ysart *et al*, 1999) reported higher intakes of 0.3 and 0.52 mg/day respectively.

According to the UK Food Standards Agency, Cr is present in a number of supplements that may only be sold under the supervision of a pharmacist, for use in malabsorptive states, conditions leading to hypoproteinaemia and perioperative nutritional support, at levels up to 0.2 mg. Cr is also present in several multivitamin and mineral food supplements at levels up to 0.6 mg (FSA, 2003).

The maximum intake of chromium has been estimated to be 0.77 mg/day, comprising up to 0.17 mg/day from food, up to 0.002 mg/day from drinking water and up to 0.6 mg/day from supplements (FSA, 2003).

Toxicological Data

Intestinal absorption of Cr III is low (up to 2%) in both humans and animals. For Cr VI, human bioavailability following oral administration of doses up to 10mg Cr VI for up to 17 days averaged up to 5.7% (Kerger et al, 1997). Most dietary Cr is not absorbed and is excreted via the faeces. Small amounts of assimilated Cr (up to 0.5 μg/day) are excreted via the urine.

Soluble Cr III compounds are moderately toxic, rodent LD_{50} values being 100-400 mg/kg. Rats fed diets containing up to 5% Cr_2O_3 for a lifetime showed no adverse effects. EPA considered that the highest dose (equivalent to 1468 mg Cr/kg/day) to be the NOEL. In a more recent dietary rat study (Anderson et al, 1997), no adverse effects were detected at 15 mg Cr III/kg/day.

The Cr VI oxyanions in aqueous solution are in pH-dependent equilibrium. At pH >6 (i.e., physiological pH), Cr VI forms the tetrahedral yellow chromate ion, CrO_4^{2-}, which is structurally similar to phosphate and sulphate and readily enters all cells via the general anion channel protein. Cr VI is readily absorbed by all tissues. The lethal oral dose of soluble chromates in humans is 50-70 mg/kg, target organs being the liver, kidney and haematopoietic system. The mechanism of action of Cr VI is thought to be by oxidation of biological tissues to form a variety of radical species including alkyl and oxygen radicals.

Toxicological studies reported on Cr VI are generally of short duration. Oral administration to rats at 10-14 mg/kg/day for 14-20 days produced several effects including reduced growth rate, increased lipid content of the liver, and alterations in the activity of liver and kidney enzymes. Longer studies, generally with no adverse effects, involve administration via drinking water at concentrations ranging from 25-200 ppm. The NOEL for a one-year rat study in which animals received water containing potassium chromate was 2.4 mg Cr/kg/day (Mackenzie *et al*, 1958).

Cr VI, but not Cr III has been shown to be genotoxic in a number of test systems and both animal studies where Cr VI has been dosed via inhalation, and human epidemiological studies have shown Cr VI to be carcinogenic in the respiratory tract. However, there is no clear evidence of carcinogenicity where chromium has been tested in rats via the oral route (ATSDR, 1998; FSA, 2003). Indeed Cr VI is reduced to Cr III in the gastrointestinal tract, and so only intakes that exceed the reducing capacity of the stomach will result in significant absorption of Cr VI across the gastrointestinal mucosa (Fleter and Dourson, 1997). Cr III (as Cr_2O_3) was non-tumorigenic when administered to rats in the diet at up to 5% Cr_2O_3.

Regulatory Assessments

US EPA oral RfDs for Cr III and Cr VI are 1.5 and 0.003 mg Cr/kg/day respectively (corresponding to 105 and 0.21mg/day based on EPA assumed 70 kg body weight).

ESADDI – set by US National Resource Council: 50-200 μg/day (corresponding to 0.7-2.9 μg/kg/day for a 70 kg adult).

The US FDA has selected a Reference Daily Intake for chromium of 120 μg/day (DHHS, 1995).

In the UK it has been recommended that dietary intakes should exceed 0.025 mg/day for adults (Department of Health, 1991). It was also noted that no adverse effects were observed at intakes of 1000-200 0mg/day Cr III.

The UK Food Standards Agency has concluded for Cr III that 'a total intake of about 0.15 mg/kg/day (or 10 mg/person) would be expected to be without adverse health effects' (FSA, 2003).

A report by the Dutch RIVM in 2001 determined a provisional Tolerable Daily Intake (TDI) of 5 μg/kg/day for oral exposure to chromium VI

For inhalation exposure to Cr VI, the Dutch RIVM has estimated that a lifetime risk of 1 in a million for lung cancer in humans was associated with a life-time exposure to 0.025 ng/m^3 (RIVM report 711701 025; 2001). For the same level of lifetime risk, the US EPA has estimated an exposure of 0.08 ng/m^3 (monograph on Cr VI in US EPA IRIS database). For a 1 in 10^5 lifetime risk the air concentrations are 0.25 and 0.8 ng/m^3, respectively.

Conclusion

Numerous regulatory assessments have concluded that oral intake of 10 mg Cr III/day (or even more) is not expected to be associated with adverse health effects. However, a conservative approach to deriving an oral PDE for chromium is proposed, employing the TDI for Cr VI of 0.005 mg/kg/day derived by the Dutch RIVM (equates to a PDE of 250 μg/day for a 50 kg individual). The rationale for this PDE is based on the following:

- Chromium residues in pharmaceuticals are typically measured as total Cr.
- Intake of chromium from pharmaceuticals is more likely to be in the form of Cr III than Cr VI
- Cr VI, not trivalent Cr III, is considered a carcinogen with genotoxic properties.
- At those levels in pharmaceuticals, Cr VI will be reduced to Cr III in the gastrointestinal tract, so that significant absorption of Cr VI is highly unlikely. In addition, at high doses (up to 10 mg Cr VI), bioavailability in man is less than 6%.
- Cr VI toxicity is believed to result from the generation of reactive intermediates and free radicals during reduction to Cr V, Cr IV and ultimately Cr III by many substances including ascorbate and glutathione in the body. Such mechanisms are considered to exhibit non-linear dose responses. The cellular effects are sub-linear at low exposures and thus a no-effect level can be assumed.
- Cr VI has not been found to be carcinogenic in the limited long-term oral in vivo studies.

For an estimate of the parenteral PDE: 25 μg/day, based on a bioavailability of 10%

An inhalation PDE for chromium VI is set at 10 ng/day. For inhalation exposure, it is relevant to take into account the cancer risk data relating to inhalation exposure of Cr VI. The lifetime inhalation concentration of Cr VI that has been associated with a lifetime risk for lung cancer of 1 in 10^5 in humans ranges from 0.25 ng/m^3 to 0.8 ng/m^3, equivalent to 5 to 16 ng/day (using 20 m^3 of air/day inhaled). An increased cancer risk of 1 in 100 000 was identified as acceptable for genotoxic impurities in Pharmaceuticals by the CHMP

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VANADIUM (V)

Introduction

V is known to exist in a variety of oxidation states (-1, 0, +2, +3, +4 and +5). The principal species in biological materials are vanadate, VO_3^-, and vanadyl, VO^{2+}. The anionic pentavalent form predominates in extracellular fluids whilst the cationic quadrivalent vanadyl ion is the most common intracellular form. Vandium is a major trace metal in fossil fuels.

Dietary Intake

UK: 13 µg/day (Evans *et al*, 1985)

USA: 6.2 - 18.3 µg/day (FDA Total Diet Study, Pennington and Jones, 1987).

V is considered by some as an essential trace mineral; vanadyl sulphate supplements (at microgram to milligram levels) are marketed to normalise blood glucose (in diabetics) and to promote muscle growth (in body builders), and are not associated with reports of any short-term adverse effects.

Toxicological Data

Most orally ingested vanadium in humans appears to be unabsorbed, only 1-5% of dose being excreted in urine. In the rat however, much higher absorption (>10%) has been reported.

A variety of toxicity studies have been undertaken in animals, and the principal target organs are the digestive system, kidneys and blood. In lifetime studies rats and mice exhibited no adverse effects when exposed to 5 ppm V (as $VOSO_4$) in drinking water (Schroeder *et al* 1970, Schroeder and Mitchener 1975), NOELs being 0.7 and 0.9 mg V/kg/day for rats and mice respectively.

Sodium metavanadate ($NaVO_3$) is considerable more toxic when given parenterally. Oral LD_{50} values were 41 and 31 mg V/kg in rats and mice respectively, whereas *ip* LD_{50}s are reported as *ca* 0.1 mg V/kg in these species. $NaVO_3$ given to rats in drinking water for 3 months produced impaired kidney function at 50 ppm and the NOEL was considered to be 10 ppm (1.32 mg/kg/day) (Domingo *et al*, 1985).

In a 6-week human study involving oral doses of 50-125 mg V/day (as vanadyl tartrate), no adverse effects were observed at the lower doses (Dimond *et al*, 1963). The NOEL is conservatively estimated as 0.5 mg V/kg/day.

Regulatory Assessments

US EPA: NOEL 0.7 mg V/kg/day (as $VOSO_4$)

A range of RfDs have been proposed based on the above NOEL and on a NOEL for $NaVO_3$ (10 ppm in a 3-month rat drinking-water study). The oral RfDs range from 0.001 mg V/kg/day (chronic RfD based on NOEL of 1.32 mg V/kg/day for $NaVO_3$ and an uncertainty factor of 1000) to 0.02 mg V/kg/day (subchronic and chronic RfD for $VOSO_4$).

UK Food Standards Agency: no estimate of acceptable daily intake established

Conclusion

In consideration of the data on dietary intakes (up to 0.3 µg V/kg/day), the use of $VOSO_4$ supplements and the US EPA RfDs, an oral PDE of 300 µg/day (6 µg V/kg/day in a 50 kg person) is proposed, based on a human NOEL of 0.5 mg/kg/day and a safety factor of 80. This recommended PDE is equivalent to 50% the subchronic RfD for $NaVO_3$ proposed by EPA and 20% of the chronic RfD for $VOSO_4$.

Estimated parenteral PDE: 30 µg/day (0.6 µg V/kg/day in a 50 kg person and based on a bioavailability of 10%)

COPPER (Cu)

Introduction

Cu is a Group IB element of the first transition series and has two main oxidation states, Cu I and Cu II. Cu is the functional component in a variety of cuproenzymes (e.g. cytochrome c oxidase, asorbic acid oxidase and superoxide dismutase); it plays an important biological role in redox reactions and in the scavenging of radicals.

Dietary Intake

Mean UK intake 1.4 mg/day; 97.5 percentile intake 3.2 mg/day (Ysart *et al*, 2000). Cu is an essential element; the US RDA is 0.9 mg/day in adult men and women aged >19 years. The Joint Expert Committee on Food Additives has recommended a PMTDI of 0.5 mg/kg/day. For the UK (Department of Health, 1991) a dietary reference value of 1.2 mg/day has been proposed for adults aged 18 years and over.

Toxicological Data

Cu is readily absorbed following oral ingestion, absorption being greatest for the most soluble salts. Data on absorption following oral intake range from 15 to 97%.

Virtually all toxicological data relate to oral Cu II, particularly $CuSO_4$. Few adequate data are available on chronic toxicity. Data are available from a number of acute and sub-chronic studies (generally up to 90 days) mainly using dietary administration. In studies on copper sulphate, chloride, carbonate and cyanide, mainly in rats, NOELs ranged from 1.7 mg Cu/kg/day (increased systolic blood pressure and increases in haemoglobin at higher dose of 9.6 mg Cu/kg/day - $CuCO_3$ used as dosing material) to 17 mg Cu/kg/day (hyperplasia and hyperkeratosis of forestomach mucosa at *ca* 30 mg Cu/kg/day – $CuSO_4$ used as dosing material). At the higher doses employed in subchronic toxicity studies the main target organs were the kidneys and liver. Microcytic anaemia occurred in rats due to depletion of iron stores. In the rat over 90 days using $Cu(CN)_2$ given by gavage, the NOEL was 5 mg Cu/kg/day.

Discussion

Copper is subject to a number of homeostatic mechanisms *in vivo* following oral ingestion that reduce the likelihood of toxic sequelae if intake exceeds the normal requirements. The mechanisms involved include binding to metallothionein, absence of significant storage, binding to albumin and transcuprein and biliary excretion.

Regulatory Assessments

US EPA: RfD (subchronic) = 0.05 mg Cu/kg/day
(NOEL of 5 mg/kg/day and assessment factor of 100)

RfD (chronic) = 0.005 mg Cu/kg/day
(same NOEL and assessment factor of 1000).

WHO Drinking Water Quality Guideline is 2 mg/L based on a NOAEL of 5 mg/kg/day in dogs.

UK: Safe Upper Level for total daily intake: 10 mg/day; at least 1 mg/day for non dietary intake.

RIVM: TDI 140 µg/kg/day

Conclusion

A PDE of 2500 µg/day or 50 µg Cu/kg/day in a 50 kg subject is considered to be suitable for both subchronic and chronic ingestion based on a subchronic oral NOEL of 5 mg/kg/day in rat and dogs with a safety factor of 100 (2 × 10 × 5 × 1 × 1)

The Estimated parenteral PDE: 5 µg Cu/kg/day (based on a bioavailability of 10%).

MANGANESE (Mn)

Introduction

Mn is an element of the first transition series (Group VIIa). It can exist in eleven oxidation states from –3 to +7, the normally encountered valences being +2 (most common form in nature), +4 (as in MnO_2) and +7 (as in permanganate ion). Mn is considered to be an essential element with a minimum intake of 2.5 mg/day.

Dietary Intake

Mean daily UK intake: 4.5 mg; 97.5 percentile daily intake: 8.2 mg. (Ysart *et al*, 1999). In an earlier review, the WHO reported the average daily consumption of Mn to range from 2.0 to 8.8 mg Mn/day (WHO, 1973). From balance studies, it was concluded that 2-3 mg/day is adequate for adults and 8-9 mg/day is 'perfectly safe'. Based on this data, the US EPA concluded that 10 mg/day (0.14 mg/kg/day) is an appropriate reference dose for manganese, with most individuals consuming about 2-5 mg Mn/day in the diet. The UK Food Standards Agency's Expert Group on Vitamins and Minerals concluded that a supplemental intake of up to 4 mg Mn/day in addition to the diet would be unlikely to produce adverse effects in the general population (FSA, 2003).

Toxicological Data

Most studies have been undertaken with Mn^{2+} ($MnCl_2$ or $MnSO_4$). Virtually all data relate to the oral route. Oral absorption is low (*ca* 3.5% in the rat). Absorbed Mn is excreted largely via the bile and is eliminated in the faeces. Mn can accumulate in the brain at high intake levels.

Carcinogenicity studies in rats and mice used dietary doses of $MnSO_4$ up to *ca* 700 and 2000 mg Mn/kg/day respectively. There was no evidence of carcinogenicity in rats but in mice the evidence was considered to be equivocal based mainly on forestomach focal squamous hyperplasia (accompanied by ulceration/erosion and inflammation). NOELs are estimated at *ca* 70 and 200 mg Mn/kg/day in rat and mouse respectively.

Genotoxicity studies on Mn^{2+} are equivocal, some positive results being obtained *in vitro* but not *in vivo*.

A number of epidemiological studies have been reported, the most extensive by Kondakis *et al* (1989) in the Northwest Peloponnesus area of Greece. This was a retrospective study of three cohorts of subjects all over 50 years exposed to water containing up to 2.3 mg/L Mn for more than 10 years. Estimated intakes via drinking water (assuming consumption of 2 L water/day) were up to 4.6 mg/day. An assessment of neurological signs and symptoms revealed higher scores (eg. for depression, fatigue and impaired reflexes) in subjects from the highest Mn area but the authors attributed the findings to the age of the subjects due to the subjectivity of some of the symptoms, lack of exposure/effect relationship and overlap with exposures shown to be negative in occupational studies.

In another retrospective study by Vieregge *et al* (1995), 2 cohorts exposed to water containing up to 2.16 mg/L Mn for 10-40 years and aged 41-86 were studied. Assuming consumption of 2 L water/day, intakes were up to 4.3 mg/day and neurological evaluation revealed no difference in scores between the two cohorts.

Regulatory Assessments

US EPA: RfD = 0.14 mg/kg/day (10 mg/day considered safe in diet, based on EPA assumed 70 kg body weight).

RfD = 0.2 mg/l (drinking water criterion based on paper by Kondakis et al).

ESADDI – set by US National Resource Food Council and Nutrition Board: 2-5 mg/day for adults.

ATSDR: 0.07 mg/kg/day (based on upper range of ESADDI).

Conclusion

Given the various assessments based on human data, results of chronic rodent studies (NOEL of 70 mg/kg/day in the rat, higher in the mouse) and estimates of dietary intakes, a conservative oral PDE for non-dietary intake of manganese of 2.5 mg Mn/day is considered to be appropriate.

Estimated parenteral PDE: 250 µg Mn/day (based on an estimated bioavailability of 10%).

Additional references for Mn

WHO (World Health Organisation). 1973. Trace Elements in Human Nutrition: Manganese. Report of a WHO Expert Committee. Technical Report Service, 532, WHO, Geneva, Switzerland. p.34-36.

FSA. 2003. Safe Upper Levels for Vitamins and Minerals. Expert group on Vitamins and Minerals. Food Standards Agency, May 2003. ISBN 1-904026-11-7.

Vieregge, P., Heinzow, B., Korf, G., Teichert, H.F., Schleifenbaum, P., Mosinger, H.U. (1995) Long term exposure to manganese in rural well water has no neurological effects. Canadian Journal of Neurological Sciences 22, 286-289.

ZINC (Zn)

Introduction

Zn is a group IIB element. It is regarded as a non-transition element since it forms no compounds in which the *d*-shell is other than full. Zn II is the predominant oxidation state; the aqua ion is quite a strong acid and is partially hydrolysed in water to hydroxy complexes. Zn forms a range of covalent organo compounds such as Zn (0) alkyls that are useful as reagents in organic synthesis. Zn has a variety of critical functions in humans: it is essential for growth and development (particularly of the brain), maintaining appetite, wound healing, immunocompetence, etc. Zn is a cofactor of the superoxide dismutase enzymes. It is an important component of DNA, acting to stabilise phosphate groups and co-ordinate with organic bases.

Dietary Intake

Mean UK intake: 11 mg/day; 97.5 percentile 20 mg/day (Ysart *et al*, 2000). Zn is an essential element and various bodies have published guidance on recommended intakes. In the US the RDA is 15 mg/day for adult men and 12 mg/day for adult women, with an additional 3 mg/day during pregnancy and 7 mg/day during lactation. UK RNIs (Reference Nutrient Intakes) for Zn are slightly lower (Department of Health, 1991).

Toxicological Data

Uptake of Zn from the gastrointestinal tract occurs by both passive diffusion and by a membrane associated carrier–mediated process. During digestion Zn is released from its dietary ligands and complexes with low-molecular-weight intestinal ligands that impede or enhance Zn bioavailability depending on their relative affinity for Zn with respect to the membrane carrier. Gastrointestinal absorption of Zn is higher when body stores are lower, and is also higher from refined diets. In the intestinal cell, following internalisation, Zn associates with metallothionein. Several metal-metal interactions are known to occur with Zn. There is mutual antagonism between Cu and Zn in terms of uptake owing to similarities in electronic configuration of their common ions ($d10$).

Elevated levels of dietary Zn can have a negative effect on Cu balance, which is exploited therapeutically to "de-copper" Wilson disease patients. Long-term oral intakes of 18-25 mg/day can interfere with Cu absorption.

A similar interaction occurs between Zn and Fe owing to mutual competition for absorption sites.

Studies in rats indicate that a high level of dietary supplementation with Zn can cause anaemia due to increased Fe turnover.

Overall, the bioavailability of oral Zn can vary widely owing to several factors, but it seems reasonable to assume that at least 10% would be absorbed on average.

The toxicological database on Zn is extensive. Rodent LD50s for soluble salts of Zn II (e.g. acetate, sulphate, nitrate) range from *ca* 100-600 mg/kg. Data from sub-chronic and chronic toxicity studies are also available, but are superseded by human data.

Regulatory Assessments

Recommendations on limits for the tolerable intake of Zn can be confusing, sometimes conflicting to some extent with recommended nutrient intakes.

WHO proposed a PMTDI of 0.3-1.0 mg/kg, corresponding to 18-60 mg/day for a 60 kg adult.

In the US the MRL and the RfD have been set at 0.3 mg Zn/kg/day (derived from a LOEL of 50 mg/day which caused slight decreases in red cell parameters in young women).

Conclusion

In consideration of the data on dietary intakes (up to 0.2 mg Zn/kg/day), the use of Zn supplements and the human LOEL of 50 mg/day, i.e. 1 mg/kg/day, an oral PDE of 13000 µg/day (260 µg Zn/kg/day in a 50 kg person) is proposed. This allows for an uncertainty factor of 4, which is more than sufficient to extrapolate the LOEL to the NOAEL. This recommended PDE is equivalent to 87% the RfD for Zn proposed by EPA.

Estimated parenteral PDE: 1300 µg/day (26 µg Zn/kg/day in a 50 kg person and based on a bioavailability of 10%)

IRON (Fe)

Introduction

Fe is a group VIII element of the first transition series. Its principal oxidation states are +2 (ferrous ion) and +3 (ferric ion). Fe is an essential human nutrient with a variety of physiological roles including those associated with haemoglobin, myoglobin, ferritin and Fe-containing enzymes.

Dietary Intake

Mean UK intake 15 mg/day; 97.5 percentile intake 26 mg/day (Ysart *et al*, 1999). The USA RDA for Fe is derived using an adequate body store of 300 mg, estimated losses of 1 mg/day in men and 1.5 mg/day in women, and an oral absorption fraction of 10-15%, leading to a recommendation of 10 mg/day for adult males and 15 mg/day for adult females, with an additional 15 mg/day recommended during pregnancy.

Toxicological Data

Fe has been studied extensively in a myriad of animal and human studies. Human toxicity is well documented, particularly in respect of fatalities in children associated with ingestion of adult Fe supplements. A single dose of 20 mg Fe/kg is sufficient to produce gastrointestinal symptoms.

Regulatory Assessments

US EPA has not derived any toxicity values for Fe.

UK A guidance value of 17 mg/day for supplemental intake was calculated.

Conclusion

In the absence of any regulatory assessment, it is proposed that the oral PDE for Fe should be set at 13 mg/day (260 µg/kg/day in a 50 kg patient), based on the US RDA and the UK guidance value for supplemental intake. This is also supported by the fact that the 97.5 percentile dietary intake is 26 mg/day. In addition, a significant proportion of dietary Fe will be in the form of haem Fe that is well absorbed compared with non-haem Fe (the form likely to be encountered as a catalyst residue in pharmaceuticals).

Estimated parenteral PDE: 1.3 mg/day (26 μg/kg/day in a 50 kg patient), based on a bioavailability of 10%.

Note on References: In the interests of brevity, monographs on the individual metal elements in Appendix 2 are not extensively referenced. Detailed bibliographies are available elsewhere, e.g., Merrill et al , 2001, and US EPA, 2001.

APPENDIX 3: EXAMPLE CALCULATIONS FOR CONCENTRATION LIMITS

In principle PDEs for metal residues were calculated as described in the Guideline for Residual Solvents CPMP/ICH/283/95 Appendix 3 with the formula

$$PDE = \frac{NOEL \times \text{Weight Adjustment}}{F1 \times F2 \times F3 \times F4 \times F5}$$

Definitions of safety factors F1 – F5 is described in the Guideline for Residual Solvents CPMP/ICH/283/95 Appendix 3

Example 1:

using the data given in Appendix 2 for Platinum oral

$$PDE = \frac{13 \text{ mg/kg/d} \times 50 \text{ kg}}{5 \times 10 \times 10 \times 10 \times 1}$$

$$PDE = 130 \text{ µg/day}$$

with	NOEL	= 13 mg/kg/d from oral rat study
	weight adjustment	= 50 kg person
	F1	= 5 for extrapolation from rats to humans
	F2	= 10 to account for variability between individuals
	F3	= 10 for study duration of less the 3 months in rodents
	F4	= 10 for severe toxicity
	F5	= 1 because NOEL was determined

As outlined in the monograph on Platinum this PDE was rounded to 100µg/day for practical reasons.

In case the daily dose of the medicinal product is not higher than 10 g/day a concentration limit of 10 ppm is acceptable. In cases the maximal daily dose of the drug product is exactly determined, the concentration limit can be calculated as describe in point 4.3. option 2:

Concentration limit = 7 ppm (using the general rounding principle)

at a maximum daily dose of 15 g/day

Example 2:

using the data given in Appendix 2 for Copper oral

$$PDE = \frac{5 \text{ mg/kg/d} \times 50 \text{ kg}}{2 \times 10 \times 5 \times 1 \times 1}$$

$$PDE = 2500 \text{ µg/day}$$

with	NOEL	= 5 mg/kg/d from oral rat and dog study
	weight adjustment	= 50 kg person
	F1	= 2 for extrapolation from dogs to humans
	F2	= 10 to account for variability etween individuals
	F3	= 5 for study duration of at least 3 months in rodents
	F4	= 1 for no severe toxicity encountered
	F5	= 1 because NOEL was determined

In case the daily dose of the medicinal product is not higher than 10 g/day a concentration limit of 250 ppm is acceptable. In cases the maximal daily dose of the drug product is exactly determined, the concentration limit can be calculated as described in point 4.3. option 2:

$$\text{Concentration (ppm)} = \frac{2500 \text{ µg/day}}{15 \text{ g/day}}$$

Concentration limit = 167 ppm (using the general rounding principle)

at a maximum daily dose of 15 g/day

or

$$\text{Concentration (ppm)} = \frac{2500 \text{ µg/day}}{5 \text{ g/day}}$$

Concentration limit = 500 ppm

at a maximum daily dose of 5 g/day