Annex VI: Toxicological information for risk assessment

This annex contains the toxicological information for each of the driving constituents considered in the risk assessment of the "PMC" UVCB substances. Data access has been provided for "toxicological information" IUCLID section 7 of the constituent IUCLID dossiers and this information is presented here without further editing.

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5. HUMAN HEALTH HAZARD ASSESSMENT

Toxicological information for the inorganic UVCB is assessed by assessing the hazard assessment (DNELs) for each individual constituent that are hazardous to humans.

5.0 Derivation of DNEL(s) and other hazard conclusions

5.0.1 Arsenic trioxide

Table 1. Hazard conclusions for workers – As_2O_3

Route	Type of effect	Hazard conclusion	Most sensitive endpoint
Inhalation	Systemic effects - Long-term	DNEL (Derived No Effect Level): 5 µg/m³	carcinogenicity (Oral)
Inhalation	Systemic effects - Acute	No hazard identified	
Inhalation	Local effects - Long-term	Medium hazard (no threshold derived)	
Inhalation	Local effects - Acute	Medium hazard (no threshold derived)	
Dermal	Systemic effects - Long-term	DNEL (Derived No Effect Level): 112 µg/kg bw/day	carcinogenicity (Oral)
Dermal	Systemic effects - Acute	No hazard identified	
Dermal	Local effects - Long-term	Medium hazard (no threshold derived)	
Dermal	Local effects - Acute	Medium hazard (no threshold derived)	
Eyes	Local effects	Medium hazard (no threshold derived)	

Further explanation on hazard conclusions:

- **Inhalation Local effects - Long-term:** DNELs for local effects are not considered to be required (qualitative assessment because of corrosive nature, or covered by high protection levels required due to long term effects

Table 2. Further explanation on DNEL derivation for workers – As_2O_3

Route / Type of effect	DNEL derivation	Assessment factors (AF) for DNEL derivation
Inhalation Systemic effects - Long-term	**DNEL derivation method:** ECHA REACH Guidance **Dose descriptor starting point:** NOAEC 15 µg/m³	**AF for remaining uncertainties:** 3 (In consideration of the oral-to-inhalation read-across, in order to cover any remaining uncertainties with respect to local effects, an assessment factor of 3 is applied.) **Overall Assessment Factor:** 3
Dermal Systemic effects - Long-term	**DNEL derivation method:** ECHA REACH Guidance	

Justification for route-to-route extrapolation:

- **Inhalation Systemic effects - Long-term:** Since arsenic-associated carcinogenicity is systemic and not essentially related to the route of entry into the body, the NOAEL value derived from epidemiological data on drinking of arsenic containing drinking water is selected as a starting point

Discussion

Introductory note:

The following major cancer risk assessments have been conducted to date (UBA, 2007):

(I) A somewhat out-of-date assessment by USEPA/IRIS (1988) based on the studies by Tseng et al. (1968, 1977) on the prevalence of skin tumours in a population in southeast Taiwan (EPA, 2007).

(II) NRC based their cancer risk assessment on the studies by Chen et al. (1985, 1992) on the incidence of tumours in bladder and lungs in southwest Taiwan, using the studies by Chiou et al. (2001) and Ferreccio et al. (2000) as supportive data.

(III) In more recent assessment, the USEPA focus on the studies by Chen et al. (1985, 1992) (Morales et al. 2000; EPA, 2001).

The German UBA has (2007) performed a comprehensive evaluation of more recent investigations on cancerogenicity of arsenic via drinking water, which are not further addressed here. The DNEL derivation in this dossier is based on more recent data.

DNEL derivation (general aspects)

For the derivation of a DNEL for diarsenic trioxide, carcinogenicity is considered the most relevant endpoint; other effects of repeated exposure to arsenic including reproduction toxicity are considered to occur at higher exposures and therefore secondary to cancer. Since rodents (in particular rats) have a metabolic pattern that differs distinctly from humans, they are less sensitive and unsuitable as models for HH risk assessment, which is why the DNEL derivation is based on human epidemiological data only.

The majority of such studies focus on effects associated with elevated arsenic intakes via drinking water. In these studies, the exact speciation (tri- or pentavalent) and relative quantification of arsenic is usually lacking. However, despite that As(III) is considered moderately more toxic than pentavalent species, the difference in toxicity is anticipated to be less than an order of magnitude, and it may also be speculated that arsenic in drinking water may be a mixture of As(III/As(V), which is why direct read-across from arsenic concentrations reported in the epidemiological studies selected for DNEL derivation is justified.

Diarsenic trioxide is soluble, and upon dissolution the absorption via ingestion or inhalation may be considered as essentially complete. Dermal absorption through human skin has been reliably measured, yielding a conservative dermal absorption factor of 2 % (Wester et al. 1993).

Carcinogenicity of arsenic is of systemic nature, and not dependant on the route of entry into the body. Thus, after long-term ingestion of elevated levels of arsenic in drinking water, cancer not only of the bladder is observed, but also of the lungs and skin.

Oral DNEL:

Several epidemiological studies have been used as point of departure for assessing the risk of cancer via drinking water intake containing arsenic. These are summarised in detail above. In a recent evaluation, the German UBA (2007) has compared all these and also summarised more recent data, concluding that despite older studies suggesting a linear dose-response, the shape of this dose-response curve and where a threshold can be established are subjects of controversy, and that overall, there is no consistent clear picture regarding the dose-response.

The major shortcomings of most such epidemiological studies are usually the limited number of subjects and thus the statistical power, as well as inadequate control of actual exposures. The most recent study by Ahsan et al. (2006) designated the Health Effects of Arsenic Longitudinal Study ("HEALS") conducted in Araihazar (Bangladesh) may be considered a step forward in that it (i) addresses a large number of subjects (n=11,746), (ii)

covers a wide range of arsenic concentrations in drinking water (0.1-864 ug/L), and (iii) exposure to arsenic was well characterised: not only the arsenic in well water was analysed, but also drinking water consumption monitored and most relevant, creatinine-adjusted urinary arsenic excretion as monitored for each participant enrolling in the study.

Using the lowest exposure group (<8 µg/L), and accounting for water intake, a cumulative arsenic index (well concentration x daily consumption x days of use/year) was derived for this group, where the arithmetic mean of intakes in this group is considered a NOAEL of 24 mg/a (LOEL 137 mg/a), corresponding to 66 and 675 µg/day for NOAEL and LOAEL, respectively. The corresponding urinary excretion in this NOAEL group is 48.3µgAs/g creatinine. Assuming that 60% of the entire arsenic intake is eliminated via urine (refer to toxicokinetic section, reference Buchet et al, 1981) and for a 60kg adult (assumed most appropriate for the Asian population studied) the default creatinine excretion is 1300mg/day, this can be recalculated to a NOAEL of 1.7µgAs/kg/day.

Given the close exposure control and the large number of participants in this study with lesions, this study is not only considered reliable and statistically robust. Since the observed lesions were not malignant, they may reasonably be considered as early indicators of arsenic intoxication.

For reasons of comparison, we note that using the same basis for their evaluations (Tseng et al., 1968 & 1977), EPA (2007), UBA (1999) and ATSDR (2005) all derived the same tolerable dose for the chronic oral exposure of arsenic, based on a NOAEL of 0.8 ug/kg bw/d to derive their RfD (EPA), TRD (UBA) and MRL (ATSDR) values.

Oral (chronic) DNEL =1.7 µgAs/kg bw/d, corresponding to 2.2 µg As_2O_3/kg bw/d

Since this systemic DNEL is derived directly from a substantial human epidemiological data base on ingestion also involving detailed biomonitoring, no modification for aspects such as bioavailability, route of administration or physiological factors is required. It is not considered to derive a different oral DNEL for the general population than for workers.

Dermal DNEL:

In consideration of the systemic nature of arsenic carcinogenicity, route-to-route extrapolation from the data obtained from drinking water studies as above to the dermal route is considered justified. For this purpose, modification of the oral DNEL derived above by considering a dermal absorption factor of 2% (refer to toxicokinetics section, reference Wester et al., 1993) is appropriate. The chronic dermal DNEL can therefore be derived as follows:

Dermal (chronic) DNEL = 1.7 µg As/kg bw/d (oral) / 2 % = 85 µg As/kg bw/d, corresponding to 112 µg As_2O_3/kg/day.

Similar to the above, this DNEL is applicable to workers and the general population.

Inhalation DNEL:

Several studies exist that document the association between inhalation exposure to arsenic and lung cancer, mores specifically to arsenic trioxide dust in air at copper smelters (Enterline et al., 1987; Lee-Feldstein et al., 1983 & 1986; Järup et al., 1989). The most recent and reliable study is considered to be the one by Lubin et al. (2008) which is an updated evaluation of the cohort of workers in the Anaconda (USA) mine. This latter investigation relates to the most recent data with the highest number of man-years and also an attempt at a more thorough exposure assessment. However, some inherent imprecision of such retrospective exposure estimates cannot be excluded.

Overall, all of the above studies have many shortcomings and therefore do not allow the precise definition of a reliable NOAEL for diarsenic trioxide and consequently of a reliable DNEL. For this reason, two alternative approaches for a DNEL (inhalation, chronic) derivation were pursued:

Approach I (oral-inhalation route-to-route extrapolation)

Since arsenic-associated carcinogenicity is systemic and not essentially related to the route of entry into the body, the NOAEL value derived from epidemiological data on drinking of arsenic containing drinking water is selected as a starting point. Thus, using the most recent study by Ahsan et al. (2006) from which an oral NOAEL of 1.7µgAs/kg/day was derived as a starting point, plus a body weight of 70 kg for a European adult and a breathing volume of 10 m^3(workers, 8-h shift), the following "uncorrected" DNEL can be derived:

Inhalation (chronic) DNEL (uncorrected) = 1.7 µg As/kg bw/d x 70 kg ÷ 10 m^3/d = 11.9 µg As/m^3, corresponding to 15µg As_2O_3/kg/day.

This DNEL does not require modification for bioavailability, since the oral bioavailability of the soluble diarsenic trioxide may be considered similarly complete as for inorganic arsenical contained in drinking water; inhalation bioavailability is also considered to be close to 100 % for material deposited in the lungs, as well the percentage that is translocated to the GI tract, for which an oral absorption of 100 % is assumed.

Apart from the consideration of the breathing volume (10m^3/shift), there is no requirement for the introduction of assessment factors for allometric scaling. However, for the general population, a different breathing volume needs to be considered, which is 20 m^3/day, resulting in an uncorrected DNEL for the general population of 6 µg As/m^3.

Assessment factors for interspecies differences, intraspecies differences, differences in duration of exposure and quality of the data base are not considered to be required. However, in consideration of the oral-to-inhalation read-across, in order to cover any remaining uncertainties with respect to local effects, an assessment factor of 3 is applied to the above derived "uncorrected" DNEL, finally yielding:

Inhalation (chronic) DNEL, workers: = 4µg As/m^3, corresponding to 5µg As_2O_3/kg/day.

Inhalation (chronic) DNEL, general population: = 2µg As/m^3, corresponding to 2.5 µg As_2O_3/kg/day.

Approach II (linear extrapolation from epidemiological data)

The German AGS (2011) has recently derived an "ERB" (Exposure Risk Relationship) for arsenic exposure in the workplace. They used the study by Lubin et al. (2008) as the basis, with a point of departure associating a workplace concentration of 135 ug/m^3 with an added risk of cancer at a level of 6.5%. In the absence of a documented threshold or mechanistic data suggesting otherwise, a linear calculation procedure (AGS, 2008) was applied acknowledging the uncertainties and inherent conservatism of this approach, leading to the following values:

- tolerance risk (4:1,000) = 8.3 ug As/m^3

- acceptance risk (4:10,000) = 0.8 ug As/m^3.

In comparison to the uncertainties associated with the exposure assessment of the data from Lubin et al (2008) and the conservatism of the linear extrapolation method used for the ERB derivation, the value derived from the Ahsan et al (2006) appears to be more reliable.

Overall summary, DNEL derivation for diarsenic trioxide

The major health concern for exposure to diarsenic trioxide is carcinogenicity, and the derived DNELs are correspondingly low. Other effects form repeated exposure including reproduction toxicity are expected to occur only at considerably higher exposure levels, which is why DNELs for these endpoints are not considered to be required.

Similarly, because of the resulting need for very tight exposure controls, DNELs for acute exposures are also not considered to be required, since acute health effects are only observed at exposures exceeding those associated with chronic effects by several orders of magnitude.

Consumer exposure to diarsenic trioxide is ruled out, since the substance is not made available to the general public as such, or in any preparation or article etc. However, since members of the general population may theoretically be exposure indirectly via the environment due to arsenic from industrial emission from the production and use of diarsenic trioxide, DNEL for the general population have also been established.

Summary of DNELs for systemic effects derived for **diarsenic trioxide**. DNELs for local effects are not considered to be required (qualitative assessment because of corrosive nature, or covered by high protection levels required due to long term effects).

	Oral	**Dermal**	**Inhalation**
Workers			
Long term, systemic	2.2 µg/kg bw/d (formally not required)	112 µg/kg bw/d	5 µg/m^3
General population			
Long term, systemic	2.2 µg/kg bw/d	112 µg/kg bw/d	2.5 µg/m^3

For the sake of comparison, we note that humans are also exposed to arsenic due to its natural occurrence. Ambient background data (non-exhaustive) is presented in an appendix to the exposure scenario document for As2O3. Typical arsenic intake data for the EU population is estimated as follows:

- via food = 50-100 µg As/d (0.7-1.4 µg As/kg bw/d); corresponding to up to 1.8 µg As_2O_3/kg bw/day
- via drinking water = 0.4-0.6 µg As/d (0.006-0.009 µg As/kg bw/d)
- via air = 0.004 µg As/d

In other words, the oral DNEL derived above is close to the total background daily intake of arsenic via food, water and air.

Table 3. Hazard conclusions for the general population – As_2O_3

Route	**Type of effect**	**Hazard conclusion**	**Most sensitive endpoint**
Inhalation	Systemic effects - Long-term	DNEL (Derived No Effect Level): 2.5 µg/m³	carcinogenicity (Oral)
Inhalation	Systemic effects - Acute	No hazard identified	
Inhalation	Local effects - Long-term	Medium hazard (no threshold derived)	
Inhalation	Local effects - Acute	Medium hazard (no threshold derived)	
Dermal	Systemic effects - Long-term	DNEL (Derived No Effect Level): 112 µg/kg bw/day	carcinogenicity (Oral)
Dermal	Systemic effects - Acute	No hazard identified	
Dermal	Local effects - Long-term	Medium hazard (no threshold derived)	
Dermal	Local effects - Acute	Medium hazard (no threshold derived)	
Oral	Systemic effects - Long-term	DNEL (Derived No Effect Level): 2.2 µg/kg bw/day	carcinogenicity (Oral)
Oral	Systemic effects - Acute	No hazard identified	
Eyes	Local effects	Medium hazard (no threshold derived)	

Table 4. Further explanation on DNEL derivation for the general population – As_2O_3

Route / Type of effect	DNEL derivation	Assessment factors (AF) for DNEL derivation
Inhalation Systemic effects - Long-term	**DNEL derivation method:** ECHA REACH Guidance **Dose descriptor starting point:** 6 µg/m³	**AF for remaining uncertainties:** 3 (In consideration of the oral-to-inhalation read-across, in order to cover any remaining uncertainties with respect to local effects, an assessment factor of 3 is applied.) **Overall Assessment Factor:** 3
Oral Systemic effects - Long-term	**DNEL derivation method:** ECHA REACH Guidance	

Justification for route-to-route extrapolation:

- **Inhalation Systemic effects - Long-term:** Since arsenic-associated carcinogenicity is systemic and not essentially related to the route of entry into the body, the NOAEL value derived from epidemiological data on drinking of arsenic containing drinking water is selected as a starting point

5.0.2 Cadmium

Table 5. Hazard conclusions for workers - Cd

Route	Type of effect	Hazard conclusion	Most sensitive endpoint
Inhalation	Systemic effects - Long-term	DNEL (Derived No Effect Level): 4 µg/m³	repeated dose toxicity (By inhalation)
Inhalation	Systemic effects - Acute	No hazard identified	
Inhalation	Local effects - Long-term	No hazard identified	
Inhalation	Local effects - Acute	No hazard identified	
Dermal	Systemic effects - Long-term	Exposure based waiving	
Dermal	Systemic effects - Acute	Exposure based waiving	
Dermal	Local effects - Long-term	Exposure based waiving	
Dermal	Local effects - Acute	Exposure based waiving	
Eyes	Local effects		

Further explanation on hazard conclusions:

- **Inhalation Systemic effects - Long-term:** To derive the endpoint specific DNELs for workers on the basis of the established OEL of 4 µg Cd/m^3 (SCOEL 2010), the NOAEL has to be corrected by assessment factors to account for the uncertainties of the database that led to the establishment of the NOAEL. As actual biomonitoring data was used to derive the OEL, and this already integrates inter-individual variation, the proposed DNEL workers, biomonitoring is therefore equivalent to the OEL, i. e. 4 µg Cd/m^3.

- **Dermal Systemic effects - Long-term:** Repeated dose toxicity via the dermal route is not expected to be significant as uptake of soluble and less-soluble cadmium compounds applied onto the skin of animals appears to be low (<1 %) (see Section 5.1.1). Also in view of the risk reduction measures which need to be taken as a result of the carcinogenicity of cadmium metal and some of the cadmium compounds, dermal toxicity is not likely to pose an issue for human health.

- **Dermal Systemic effects - Acute:** Acute toxicity via the dermal route is not expected to be significant as uptake of soluble and less-soluble cadmium compounds applied onto the skin of animals appears to be low (<1 %) (see Section 5.1.1). Also in view of the risk reduction measures which need to be taken as a result of the carcinogenicity of cadmium metal and some of the cadmium compounds, acute dermal toxicity is not likely to pose an issue for human health.

- **Dermal Local effects - Long-term:** Repeated dose toxicity via the dermal route is not expected to be significant as uptake of soluble and less-soluble cadmium compounds applied onto the skin of animals appears to be low (<1 %) (see Section 5.1.1). Also in view of the risk reduction measures which need to be taken as a result of the carcinogenicity of cadmium metal and some of the cadmium compounds, dermal toxicity is not likely to pose an issue for human health.

- **Dermal Local effects - Acute:** Acute toxicity via the dermal route is not expected to be significant as uptake of soluble and less-soluble cadmium compounds applied onto the skin of animals appears to be low (<1 %) (see Section 5.1.1). Also in view of the risk reduction measures which need to be taken as a result of the carcinogenicity of cadmium metal and some of the cadmium compounds, acute dermal toxicity is not likely to pose an issue for human health.

Table 6. Further explanation on DNEL derivation for workers - Cd

Route / Type of effect	DNEL derivation	Assessment factors (AF) for DNEL derivation
Inhalation Systemic effects - Long-term	**DNEL derivation method:** ECHA REACH Guidance **Dose descriptor starting point:** NOAEC	**Overall Assessment Factor:** 1

Table 7. Hazard conclusions for the general population - Cd

Route	Type of effect	Hazard conclusion	Most sensitive endpoint
Inhalation	Systemic effects - Long-term	No-threshold effect and/or no dose-response information available	
Inhalation	Systemic effects - Acute	No-threshold effect and/or no dose-response information available	
Inhalation	Local effects - Long-term	No-threshold effect and/or no dose-response information available	
Inhalation	Local effects - Acute	No-threshold effect and/or no dose-response information available	
Dermal	Systemic effects - Long-term	Exposure based waiving	
Dermal	Systemic effects - Acute	Exposure based waiving	
Dermal	Local effects - Long-term	Exposure based waiving	
Dermal	Local effects - Acute	Exposure based waiving	
Oral	Systemic effects - Long-term	DNEL (Derived No Effect Level): 1 µg/kg bw/day	repeated dose toxicity
Oral	Systemic effects - Acute	No-threshold effect and/or no dose-response information available	

Route	Type of effect	Hazard conclusion	Most sensitive endpoint
Eyes	Local effects		

Further explanation on hazard conclusions:

- **Inhalation Systemic effects - Long-term:** inhalation DN(M) EL not applicable for general population

- **Inhalation Systemic effects - Acute:** inhalation DN(M) EL not applicable for general population

- **Inhalation Local effects - Long-term:** inhalation DN(M) EL not applicable for general population

- **Inhalation Local effects - Acute:** inhalation DN(M) EL not applicable for general population

- **Dermal Systemic effects - Long-term:** Repeated dose toxicity via the dermal route is not expected to be significant as uptake of soluble and less-soluble cadmium compounds applied onto the skin of animals appears to be low (<1 %) (see Section 5.1.1). Also in view of the risk reduction measures which need to be taken as a result of the carcinogenicity of cadmium metal and some of the cadmium compounds, dermal toxicity is not likely to pose an issue for human health.

- **Dermal Systemic effects - Acute:** Acute toxicity via the dermal route is not expected to be significant as uptake of soluble and less-soluble cadmium compounds applied onto the skin of animals appears to be low (<1%) (see Section 5.1.1). Also in view of the risk reduction measures which need to be taken as a result of the carcinogenicity of cadmium metal and some of the cadmium compounds, acute dermal toxicity is not likely to pose an issue for human health.

- **Dermal Local effects - Long-term:** Repeated dose toxicity via the dermal route is not expected to be significant as uptake of soluble and less-soluble cadmium compounds applied onto the skin of animals appears to be low (<1 %) (see Section 5.1.1). Also in view of the risk reduction measures which need to be taken as a result of the carcinogenicity of cadmium metal and some of the cadmium compounds, dermal toxicity is not likely to pose an issue for human health.

- **Dermal Local effects - Acute:** Acute toxicity via the dermal route is not expected to be significant as uptake of soluble and less-soluble cadmium compounds applied onto the skin of animals appears to be low (<1 %) (see Section 5.1.1). Also in view of the risk reduction measures which need to be taken as a result of the carcinogenicity of cadmium metal and some of the cadmium compounds, acute dermal toxicity is not likely to pose an issue for human health.

- **Oral Systemic effects - Long-term:** To derive the endpoint specific DNEL for the general population on the basis of general population monitoring data 1µg Cd/kg bw/day (ca. 2µg Cd/g creatinin) and applying an assessment factor of 1, results in a DNEL for the general population of 1µg Cd/kg bw/day. All assessment factors are equivalent to 1 as actual biomonitoring data was used to derived the starting point, which already integrates inter-individual variation and accounts for lifetime exposure.

- **Oral Systemic effects - Acute:** Long term systemic oral DNEL considered sufficient to ensure that these effect do not occur

Discussion

Given the wealth of available animal and human data, the calculation of DNELs for general population can be done using different approaches. In the following section, DNELs are derived based on the results of 1) long-term animal testing and 2) monitoring data. The resulting values are then compared and discussed.

$DNEL_{general\ population}$ derived from animal data

As there is currently no conclusive evidence from human studies that cadmium acts as a carcinogen following oral exposure, DNELs for the general population can be calculated based on data from repeated-dose toxicity studies in animals. The lowest oral NOAEL presented in Section 5.11.1 corresponds to **0.12 mg Cd/kg bw/day** from a 9 year study in monkey (Masoaka *et al.,* 1994). Using this value as a starting point and applying the default assessment factors proposed in Table R.8-6 of the 'REACH guidance on information requirements and chemical safety assessment, Chapter R.8' yields the following results:

Derivation of cadmium $DNEL_{general\ population}$ based on animal data

	Value	**Comment**
Starting point	0.12 mg/kg bw/day	NOAEL from a 9 year repeated dose oral toxicity study in monkey
Assessment factor	2	Interspecies difference, allometric scaling monkey - human
	2.5	Interspecies difference - remaining differences
	10	Intraspecies variation, general population
	1	Exposure duration (9 years; chronic)
	1	Dose-response
	1	Quality of whole database
$DNEL_{general\ population}$	0.0024 mg Cd/kg bw/day	

The resulting **$DNEL_{general\ population}$** is therefore equivalent to **0.0024 mg (2.4 µg) Cd/kg bw/day**.

$DNEL_{general\ population}$ derived from general population monitoring

As discussed in Section 5.6.2, data from several large general population studies indicate that early renal effects (urinary excretion of low molecular weight proteins, occurring before the onset of overt clinical manifestations of kidney disease) can be detected in the general population for Cd-U around 2 µg Cd/g creatinine. In the Belgian Cadmibel study (Buchet *et al.,* 1990), a urinary excretion of 2 µg/24 h (i. e. roughly 2 µg/g creatinine according to SCOEL, 2010) is estimated to correspond to a mean renal cortex concentration of 50 ppm (wet weight), which in non-smokers would be reached after 50 years of oral ingestion of approximately **1 µg Cd/kg bw/day**. This value of 1 µg Cd/kg bw/day can be used as the starting point for estimation of the $DNEL_{general\ population}$.

As actual biomonitoring data was used to derive the starting point, and this already integrates inter-individual variation and accounts for lifetime exposure. The resulting **$DNEL_{general\ population}$** is therefore equivalent to**1 µg Cd/kg bw/day**(i. e. ca. 2 µg Cd/g creatinine).

Discussion

The $DNEL_{general\ population}$ derived using either animal or human monitoring data are in good accordance (i.e. 2.4 and 1 µg Cd/kg bw/day, respectively), with the second approach yielding a slightly lower value. As a comparison, the WHO calculate that, in order that levels of cadmium do not exceed 50 µg/g in renal cortex, assuming an absorption rate of 5% and a daily excretion of 0.005 % of body burden, total intake should not exceed about**1 µg/kg bw/day** continuously for 50 years (WHO, 1987).

5.0.3 Nickel sulfate

Table 8. Hazard conclusions for workers – $NiSO_4$

Route	Type of effect	Hazard conclusion	Most sensitive endpoint
Inhalation	Systemic effects - Long-term	DNEL (Derived No Effect Level): 131.8 µg/m³	developmental toxicity / teratogenicity (By inhalation)
Inhalation	Systemic effects - Acute	DNEL (Derived No Effect Level): 42 mg/m³	acute toxicity (By inhalation)
Inhalation	Local effects - Long-term	DNEL (Derived No Effect Level): 131.8 mg/m³	repeated dose toxicity
Inhalation	Local effects - Acute	DNEL (Derived No Effect Level): 1.85 mg/m³	repeated dose toxicity
Dermal	Systemic effects - Long-term	No hazard identified	
Dermal	Systemic effects - Acute	No hazard identified	
Dermal	Local effects - Long-term	DNEL (Derived No Effect Level): 1.16 µg/cm²	sensitisation (skin)
Dermal	Local effects - Acute	Low hazard (no threshold derived)	
Eyes	Local effects	No hazard identified	

Further explanation on hazard conclusions:

- **Dermal Local effects - Acute:** Not irritant at concentration limit < 20 %

Table 9. Further explanation on DNEL derivation for workers – $NiSO_4$

Route / Type of effect	DNEL derivation	Assessment factors (AF) for DNEL derivation
Inhalation Systemic effects - Long-term	**DNEL derivation method:** SCOEL proposed OEL of 50 µg Ni/m³	
Inhalation Systemic effects - Acute	**DNEL derivation method:** ECHA REACH Guidance **Dose descriptor starting point:** NOAEC 316.5 mg/m³	**AF for other interspecies differences:** 2.5 **AF for intraspecies differences:** 3 **Overall Assessment Factor:** 7.5
Inhalation Local effects - Long-term	**DNEL derivation method:** SCOEL proposed OEL of 50 µg Ni/m³	
Inhalation Local effects - Acute	**DNEL derivation method:** ECHA REACH Guidance **Dose descriptor starting point:** LOAEC	**Overall Assessment Factor:** 1
Dermal Local effects - Long-term	**DNEL derivation method:** ECHA REACH Guidance **Dose descriptor starting point:** NOAEL	**Overall Assessment Factor:** 1

Discussion

Note 1. Exposures are always given in terms of mg nickel and NOT as mg substance

Note 2. All the values (including the dermal one) are provided in the table below.

Note 3. In cases where existing standards (OELs in case of workers, ambient air standards in case of general public) are used instead of DNEL/DMEL, the fields for Assessment factors and Dose descriptor Starting Points were left blank. Further information on the Standard derivation is contained in the documents referenced in the Table below.

Nickel sulphate hexahydrate DN(M) ELs for workers

Exposure pattern	**Route**	**Descriptor**	**DNEL / DMEL[a]**	**AF**	**Corrected Dose descriptor**	**Most sensitive endpoint**	**Justification**
Acute - systemic effects	Dermal						Not relevant, negligible absorption
Acute - systemic effects	Inhalation	DNEL (Derived No Effect Level)	16 mg Ni/m³ (MMAD = 3 µm) [b]	7.5[c]	NOAEC: 120 mg Ni/m³ (MMAD = 3 µm)	acute toxicity (mortality)	See footnotes
Acute - local effects	Dermal						No available data to derive DNEL. Not irritating <20% See footnote (f)
Acute - local effects	Inhalation	DNEL (Derived No Effect Level)	0.7 mg Ni/m³ (MMAD < 4 µm) [b]	1[d]	LOAEC: 0.7 mg Ni/m³ (MMAD < 4 µm)	repeated dose toxicity (lung inflammation)	See footnotes
Long-term - systemic effects	Dermal						Not relevant, negligible absorption
Long-term - systemic effects	Inhalation	DNEL (Derived No Effect Level)	0.05 mg Ni/m³ Inhalable fraction[e]			developmental toxicity	See footnotes
Long-term - local effects	Dermal	DNEL (Derived No Effect Level)	0.00044 mg Ni/cm²[f]	1[g]	NOAEL:0.00044 mg Ni/cm²	sensitisation (skin)	See footnotes
Long-term - local effects	Inhalation	DNEL (Derived No Effect Level)	0.05 mg Ni/m³ Inhalable fraction[e]			carcinogenicity and repeated toxicity (respiratory tract-inhalation)	See footnotes

a. The approaches used in the derivation of DNELs are described in a report prepared by VITO Consultancy (Belgium) and included in Appendices C1andC3.

b. Acute DNELs based on animal inhalation studies are reported as mg Ni/$m^3$of an aerosol of the same particle size as used in the animal studies. These DNELs cannot be directly compared to workplace aerosols of different particle size. The proper comparisons should take into account the equivalent deposited doses per unit surface area in the respiratory tract of rats exposed to experimental aerosols and in humans exposed to workplace aerosols. For more details see Appendix C2. Therefore this respirable size DNEL provides a very conservative estimate for an inhalable size DNEL. When this acute respirable DNEL is compared to an inhalable exposure, a conservative risk characterization ratio (RCR) will be derived.

c. Assessment Factor (AF) = 7.5. [AF interspecies differences in susceptibility (AS) = 1 for exposures expressed as concentrations mg/m^3, and for lethal effects; AF interspecies remaining differences in susceptibility for respiratory tract = 2.5, ECHA Guidance Table R. 8-6 Default assessment factors; AF intraspecies differences in susceptibility =3 for substances that do not undergo metabolism, ECETOC (2003, 2010), see Appendix C2 section C2.3.3 for more detailed justification; Overall AF = 2.5 x 3 =7.5]. Uncertainty in DNEL derivation related to differences in particle size between animal aerosol (3 µm) and human exposure (< 100 µm), differences in susceptibility of acute toxicity effects of nickel in rats versus human, and TK and TD differences among workers, are considered to be accounted for by the use of an AF of 7.5

d. AF = 1. [AF interspecies difference (AS) = 1 local respiratory effects. AF interspecies difference in susceptibility = 1 (for respiratory toxicity effects after inhalation of particles of nickel or most metal-containing substances in the respirable range, 1-5 µm diameter, rats seem to be more susceptible to toxicity effects than mice, primates or humans. See Appendices C1andC3, and C2section C2.3.3); AF intraspecies differences in susceptibility=3 for substances that do not undergo metabolism, ECETOC (2003, 2010), see Appendix C2section C2.3.3 for more detailed justification of AF. AF for conversion of LOAEC to NAEC=3, ECHA Guidance recommends a factor between 1 and 10, 3 was selected for local respiratory effects and based on steep dose-response for nickel toxicity. An AF for exposure duration= 1/9was applied (as used in the European Union Risk Assessment for Nickel Sulphate, 2008-2009), since the duration is longer than in an acute study (12 exposures of 6 hours each during 16 days versus a single 4-hour exposure in an acute guidance study). The European Union Risk Assessment calculated intra and interspecies uncertainty factors and then multiplied them by 1/9 to calculate a final factor, after balancing all the study duration considerations. Overall AF= 1 X 3 X 3 X 1/9 = 1]. Uncertainty in DNEL derivation related to different length of exposure of starting animal study compared to standard acute toxicity tests (12 x 6 hours versus 1 x 4 hours), differences in particle size between animal aerosol < 4 um) and human exposure (< 100 um), calculation of NAEC from observed LOAEC, differences in susceptibility of local respiratory toxicity effects of nickel in rats versus human, and TK and TD differences among workers are considered be balanced and accounted for by the use of an AF of 1.

e. The justification for the use of an inhalable OEL of 0.05 mg Ni/m^3 is provided in Appendix C2. This value is based on the SCOEL proposed inhalable OEL for nickel compounds of 0.01 mg Ni/m^3 (June 2011) with further adjustments for differences in particle size distributions between animal experiments and workplace exposures and differences in sampling efficiency between 37-mm and inhalable samplers. The SCOEL value was based on epidemiological data on cancer effects. The registrant-derived inhalable value of 0.05 mg Ni/m^3 is based on toxicity local effects observed in the lungs of rats after inhalation and carcinogenicity effects in the respiratory tract observed in human studies. Both registrant and SCOEL consider nickel compounds to be genotoxic carcinogens with a practical threshold. These values are also protective against possible reproductive effects. For detailed description of the DNEL derivation based on developmental reproductive effects, see Appendices C1andC3.

f. The DNEL for dermal sensitization/elicitation is based on a patch test study with Ni sulphate where exposure lasted for 48 h under occlusion. This value is likely to overestimate risk compared to workplace 8 h exposure without occlusion. This DNEL is protective of both acute and long-term dermal exposures.

g. AF =1. Study done in humans, 48 hours under occlusion. Study was done with a susceptible population.

Appendix C1= Derivation of DNELs for 4 Reference Ni substances

Appendix C2= Background Document in Support of Long-term Inhalable DNELs for Nickel Metal and Nickel Compounds

Appendix C3= Excel table of DNEL derivations –nickel sulphate

Table 10. Hazard conclusions for the general population – $NiSO_4$

Route	Type of effect	Hazard conclusion	Most sensitive endpoint
Inhalation	Systemic effects - Long-term	DNEL (Derived No Effect Level): 52.7 ng/m³	developmental toxicity / teratogenicity
Inhalation	Systemic effects - Acute	DNEL (Derived No Effect Level): 25.3 mg/m³	acute toxicity
Inhalation	Local effects - Long-term	DNEL (Derived No Effect Level): 52.7 ng/m³	
Inhalation	Local effects - Acute	DNEL (Derived No Effect Level): 1.1 mg/m³	repeated dose toxicity
Dermal	Systemic effects - Long-term		
Dermal	Systemic effects - Acute		
Dermal	Local effects - Long-term		
Dermal	Local effects - Acute		
Oral	Systemic effects - Long-term	DNEL (Derived No Effect Level): 0.06 mg/kg bw/day	developmental toxicity / teratogenicity
Oral	Systemic effects - Acute	DNEL (Derived No Effect Level): 0.03 mg/kg bw/day	sensitisation (skin)
Eyes	Local effects	No hazard identified	

Further explanation on hazard conclusions:

- **Inhalation Systemic effects - Long-term:** See Discussion
- **Inhalation Systemic effects - Acute:** See Discussion
- **Inhalation Local effects - Long-term:** See Discussion
- **Inhalation Local effects - Acute:** See Discussion
- **Dermal Systemic effects - Long-term:** Not relevant, negligible absorption
- **Dermal Systemic effects - Acute:** Not relevant, negligible absorption
- **Dermal Local effects - Long-term:** Not relevant (negligible exposure)
- **Dermal Local effects - Acute:** Not relevant (negligible acute exposure)
- **Oral Systemic effects - Long-term:** See Discussion
- **Oral Systemic effects - Acute:** See Discussion

Table 11. Further explanation on DNEL derivation for the general population – $NiSO_4$

Route / Type of effect	DNEL derivation	Assessment factors (AF) for DNEL derivation
Inhalation Systemic effects - Acute		**Overall Assessment Factor:** 12.5
Inhalation Local effects - Long-		**Overall Assessment Factor:**

Route / Type of effect	DNEL derivation	Assessment factors (AF) for DNEL derivation
term		
Inhalation Local effects - Acute		**Overall Assessment Factor:** 1.7
Oral Systemic effects - Long-term	**Dose descriptor starting point:** NOAEL	**Overall Assessment Factor:** 50
Oral Systemic effects - Acute	**Dose descriptor starting point:** LOAEL	**Overall Assessment Factor:** 1

Discussion

Note 1. Exposures are always given in terms of mg nickel and NOT as mg substance

Note 2. All the values (including the inhalation one) are provided in the table below:

Note 3. In cases where existing standards (OELs in case of workers, ambient air standards in case of general public) are used instead of DNEL/DMEL, the fields for Assessment factors and Dose descriptor Starting Points were left blank. Further information on the Standard derivation is contained in the documents referenced in the Table below.

Nickel sulphate hexahydrate DN(M) ELs for general population (MvE)

Exposure pattern	Route	Descriptor	DNEL / DMEL[a]	AF	Corrected Dose descriptor	Most sensitive endpoint	Justification
Acute - systemic effects	Dermal						Not relevant, negligible absorption
	Inhalation	DNEL (Derived No Effect Level)	9.6 mg Ni/m^3[b]	12.5[c]	NOAEC: 120 mg Ni/m^3	acute toxicity (mortality)	See footnotes
	Oral	DNEL (Derived No Effect Level)	0.012 mg Ni/kg/day[d]	1	LOAEL= 0.012 mg Ni/kg/day	exacerbation of existing dermatitis	See footnotes
Acute - local effects	Dermal						Not relevant, negligible dermal exposure
	Inhalation	DNEL (Derived No Effect Level)	0.4 mg Ni/m^3[b]	1.7[e]	LOAEC: 0.7 mg Ni/m^3	repeated dose toxicity (lung inflammation)	See footnotes
Long-term - systemic effects	Dermal						Not relevant, negligible absorption
	Inhalation	DNEL (Derived No Effect Level)	0.00002 mg Ni/m^3[f]			reproductive developmental toxicity	See footnotes
	Oral		0.02 mg Ni/kg/day	50[g]	LOAEC: 1.1 mg Ni/kg/day	reproductive developmental toxicity	See footnotes

Exposure pattern	Route	Descriptor	DNEL / DMEL[a]	AF	Corrected Dose descriptor	Most sensitive endpoint	Justification
Long-term - local effects	Dermal						Not relevant, negligible exposure
	Inhalation	DNEL (Derived No Effect Level)	0.00002mg Ni/m^{3}[f]		CSTEE (ambient air standard) = 0.00002mg Ni/m^{3}	repeated dose toxicity (lung inflammation) carcinogenicity	See footnotes

a. See Appendices C1andC3for more details on NOAEL identification and DNEL derivation.

b. This DNEL value for acute effects after inhalation is superseded by the CSTEE, EU Scientific Committee on Toxicity, Ecotoxicity and the Environment (2001) proposed ambient air guidance value of 0.00002 mg Ni/m^{3}as discussed in Appendices C1and C3 and Appendix D5. The long term DNEL is protective against systemic effects like mortality and local toxicity and carcinogenicity effects in the respiratory tract.

c. Assessment Factor (AF) = 12.5. [AF interspecies differences in susceptibility (AS) = 1 for exposures expressed as concentrations mg/m^{3}, and for lethal effects; AF interspecies remaining differences in susceptibility for respiratory tract = 2.5, ECHA Guidance Table R. 8-6 Default assessment factors; AF intraspecies differences in susceptibility =5 for substances that do not undergo metabolism, ECETOC (2003, 2010), see Appendix C2 section C2.3.3 for more detailed justification; Overall AF = 1 x 2.5 x 5 =12.5]. Uncertainty in DNEL derivation related to differences in particle size between animal aerosol (3 µm) and human exposure (PM10, PM2.5), differences in susceptibility of acute toxicity effects of nickel in rats versus human, and TK and TD differences among workers, are considered to be accounted for by the use of an AF of 12.5.

d. This DNEL value was considered by WHO (World Health Organization, 2007. Background document for development of WHO Guidelines for Drinking-water Quality. © World Health Organization, Geneva) in the derivation of the Tolerable Daily Intake for nickel. The population at risk of having an exacerbation of dermal symptoms after oral challenge consists of patients with severe nickel sensitisation. Less sensitive nickel allergic patients and the non-allergic population will not experience exacerbation of dermal symptoms or appearance of dermal symptoms after oral nickel ion intake (e. g., Ni ion in water). WHO considered an AF =1 in developing drinking water guidelines for nickel based on the Nielsen study. "The LOAEL established after provocation of fasted patients with an empty stomach is 12 µg/kg of body weight (Nielsen et al., 1999). Because this is based on a highly sensitive population, it is not necessary to include an additional uncertainty factor. Based on these data, the guideline value, to allow for nickel-sensitive individuals, can be calculated as 70 µg/litre (rounded value), assuming a 60-kg adult drinking 2 litres of water per day and allocating 20% of total daily intake to drinking-water. Although this is very close to the acute LOAEL established by Nielsen et al. (1999), the absorption from drinking-water is 10- to 40-fold higher than the absorption from food, and basing the total acceptable intake for oral challenge from studies using drinking-water on an empty stomach in fasted patients can be considered a worst-case scenario." This value was considered to be protective of sensitive subpopulations, including most nickel sensitive individuals, pregnant women and children. Uncertainty in DNEL derivation is related to response of Ni-sensitized volunteers with hand eczema to the oral challenge with12 µg Ni/kg of body weight (45 % had exacerbation of existing dermatitis). This is considered to be balanced by the fact that absorption of Ni was maximized in this study (volunteers had been in low-Ni diet and were exposed under fasting conditions) and that the proportion of Ni-sensitive individuals (e.g., 10 %) that present with hand eczema at any given time is expected to be very low.

e. AF = 1.7 [AF interspecies difference (AS) = 1 local respiratory effects. AF interspecies difference in susceptibility = 1 (for respiratory toxicity effects after inhalation of particles of nickel or most metal-containing substances in the respirable range, 1-5 µm diameter, rats seem to be more susceptible to toxicity effects than mice, primates or humans. See Appendices C1andC3); AF intraspecies differences in susceptibility=5for substances that do not undergo metabolism, ECETOC (2003, 2010), see Appendix C2 section C2.3.3 for more detailed justification of AF. AF for conversion of LOAEC to NAEC=3, ECHA Guidance recommends a factor between 1 and 10, 3 was selected for local respiratory effects and based on steep dose-response for nickel toxicity. An AF for exposure duration= 1/9 was applied (as used in the European Union Risk Assessment for Nickel Sulphate, 2008-2009), since the duration is longer than in an acute study (12 exposures of 6 hours each during 16 days versus a single 4-hour exposure in an acute guidance study). The European Union Risk Assessment calculated intra and interspecies uncertainty factors and then multiplied them by 1/9 to calculate a final factor, after balancing all the

study duration considerations. Overall AF= 1 X 5 X 3 X 1/9 = 1.7]. Uncertainty in DNEL derivation related to different length of exposure of starting animal study compared to standard acute toxicity tests (12 x 6 hours versus 1 x 4 hours), differences in particle size between animal aerosol < 4 um) and human exposure (PM10, PM2.5), calculation of NAEC from observed LOAEC, differences in susceptibility of local respiratory toxicity effects of nickel in rats versus human, and TK and TD differences among workers are considered be balanced and accounted for by the use of an AF of 1.7.

f. We used the CSTEE, EU Scientific Committee on Toxicity, Ecotoxicity and the Environment (2001) ambient air recommended nickel value of 20 ng Ni/m^3 instead of a DMEL based on carcinogenicity or a DNEL based on long term-local respiratory effects. The CSTEE value is based on considerations of both respiratory toxicity and carcinogenicity and it is also protective from systemic exacerbation of dermatitis in sensitized individuals (see Appendix C1andAppendix D5).

g. AF= 50 [AF interspecies difference other =2.5; AF interspecies AS =4 (rat-human) according to ECHA Guidance Table R. 8-6 Default assessment factors; AF intraspecies differences in susceptibility=5 for substances that do not undergo metabolism, ECETOC (2003, 2010), see Appendix C2 section C2.3.3 for more detailed justification; AF to account for differences in exposure duration=1; Overall AF = 2.5 x 4 x 5 = 50.; the inclusion of a factor of 2-3 for severity of effects is not justified since an exposure level corresponding to 2-fold the NOAEL in the second generation study with nickel sulphate was considered by some experts as the NOAEL for the observed effects. See Appendix C3].

Sensitive subpopulations. Sensitive subpopulations are not separately addressed as the oral DNEL values used correspond to the TDI calculated by WHO for the general public (this value was based on the response of a sensitive subpopulation). The inhalation DNEL value used corresponds to the ambient air guidance value derived by CSTEE for the EU general public. This value was derived based on a linear extrapolation for possible cancer effects. There is now acceptance that nickel compounds have a practical threshold for carcinogenicity. Therefore, this value is very conservative and it is expected to protect the most sensitive individuals in the population. Although soluble nickel compounds carry a CLP classification as Resp. Sens. 1; H334, the occurrence of nickel-induced asthma among exposed workers is rare and there are only a few cases pointing to a workplace-related asthmatic disease. For this reason, deriving DNELs that protect workers or the general population from respiratory toxicity are considered to be protective of any possible sensitization effects as well.

Appendix C1= VITO report: Derivation of DNELs for 4 Ni substances

Appendix C3= Excel table of DNEL derivations –nickel sulphate

Appendix D5= Man Via the Environment Risk Assessment

5.0.4 Lead

In general: No local effects were identified. All DNEL's are based upon systemic biomarkers of exposure and not upon external exposure. DNEL's were further deemed to be inappropriate for acute toxicity endpoints since lead and lead compounds did not exhibit acute toxicity in appropriately designed GLP quality studies.

Discussion - worker:

NOAEL's were used to derive DNEL's with the following rationale being applied to interpretation of the health effects data.

1. Correction of dose descriptors is not needed since data are based upon a systemic measure of exposure (lead in blood) in humans that eliminates the need for route to route extrapolations or other corrections to the dose descriptors. The toxicity of systemic lead is mediated by the lead cation and is independent of the original speciation of the lead compound to which exposure occurred. For inorganic lead and its' compounds, toxicity indexed to internal blood lead can generally be evaluated independent of the speciation of the compound to which exposure originally occurred.
2. The NOAEL's were identified from multiple (in some case in excess of 100) scientific studies of human populations. This has permitted detailed evaluation of issues such as age, gender, ethnicity, intensity of exposure and duration of exposure that can be sources of uncertainty in effects assessment. Given that extrapolations are not made from animal studies and that specific NOAEL's have been derived for

susceptible subpopulations there is no need to correct for inter-species variability with Assessment Factors.

3. Separate NOAEL's have been developed for sensitive subpopulations and accommodate intra-species variability that might otherwise require the use of an Assessment factor. NOAEL's derived for different health endpoints are shown in the following table. Those NOAEL's that are the lowest for a given subpopulation are shown in bold text. From this table it can be seen that NOAEL's have been proposed for the most sensitive subsets of the population and define blood lead levels protective against subtle effects. Whereas NOAEL's indexed to endpoints that constitute a material impairment of health might merit consideration of an Assessment Factor greater than "1", the NOAEL's derived in this assessment protect against preclinical effects that precede material health impairment.

Table 12. NOAEL's and proposed blood lead levels for different exposed populations - Pb

Health effects endpoint	NOAEL	Exposed population
Renal system effects	60 µg/dL	Adult
Haematological effects	50 µg/dL	Adults
Reproductive effects (male)	45 µg/dL	Male Adults
Nervous system effects (adult)	**40 µg/dL**	**Adults**
Reproductive effects (female)	30 µg/dL	Women of child-bearing capacity
Nervous system effects (f**oetal effects) during pregnancy**	**10 µg/dL**	**Pregnant women/women of child-bearing capacity**

4. The most sensitive NOAEL's in adults protect against effects known to be reversible if exposure is reduced.
5. The dose response for lead toxicity is steep and increases the precision with which NOAEL's can be identified. For example, although sub-clinical manifestations of neurotoxicity may be manifested in adults in the range of 40 – 50µg/dL, significant cognitive impairment would be expected to result from a doubling of blood lead.
6. Consideration was given to whether Assessment Factors might be needed to guard against more significant health effects that might occur at higher blood lead levels. This consideration was primarily relevant to the occupational setting but was considered unnecessary since blood lead levels in the occupational setting are routinely monitored – risk management protocols already in place should preclude significant exceedance of the NOAEL's. Furthermore, the NOAEL's are indexed to blood lead and not to external measures of exposure. The toxicokinetics of lead are highly non-linear – particularly in the exposure ranges that characterise the workplace. Simulations from a physiologically based model of lead determined that a doubling of occupational blood lead in the workplace would require a disproportionately higher increase in external exposure. The toxicokinetics of lead are such that Assessment Factors are not need afford protection against exposures that might exceed NOAEL's for more significant health effects since in the increase in external exposure required would be large and prevented by medical surveillance and biological monitoring programs.
   Combined, the preceding indicated that the NOAEL's derived here are both conservative and protective of health. The majority of NOAEL's can thus be converted to DNEL's with an Assessment Factor of "1". Separate DNEL's indexed to acute toxicity are not needed. Animal testing indicates that lead is not acutely toxic. Moreover, the DNEL's for repeated dose toxicity are far lower than those that might be considered under acute exposure circumstances.

   No DNEL/DMEL has been proposed for mutagenicity. In vitro doses required to produce effects (via what are believed to be indirect, thresholded mechanisms) are far higher than those that possess physiological relevance and in vivo testing via physiologically relevant administration routes is considered to be negative.

   No DNEL/DMEL has been proposed for cancer. Lead induces tumours (generally of the kidney) via what is believed to be an indirect mechanism that is likely nongenotoxic and a multi-step process involving sustained renal toxicity accompanied by prolonged forced cell proliferation. The generally negative genotoxicity profile of lead is consistent with this rationale, as are the generally negative epidemiology studies of workers occupationally exposed to lead. If kidney cancer were to be induced in humans it would likely proceed via a thresholded non-genotoxic mechanisms that requires exposures higher than those that produce significant renal damage. A DNEL/DMEL for cancer, if derived, would be higher than the NOAEL's that have been derived for neurological function in adults.

   The DNEL's derived for different sub-sets of the population in accordance with the preceding are summarised below in terms of lead in blood concentrations.

Table 13. DNEL's Used for Occupational Exposure Assessment - Pb

Subpopulation	DNEL	Health Basis of DNEL
Pregnant Woman	10 ug/dL	Developmental toxicity affecting cognitive development
All Other Adults	40 ug/dL	Neuropsychological function

Discussion – general population:

NOAEL's were used to derive DNEL's with the following rationale being applied to interpretation of the health effects data.

1. Correction of dose descriptors is not needed since data are based upon a systemic measure of exposure (lead in blood) in humans that eliminates the need for route to route extrapolations or other corrections to the dose descriptors.
2. The NOAEL's were identified from multiple (in some case in excess of 100) scientific studies of human populations. This has permitted detailed evaluation of issues such as age, gender, ethnicity, intensity of exposure and duration of exposure that can be sources of uncertainty in effects assessment. Given that extrapolations are not made from animal studies and that specific NOAEL's have been derived for susceptible subpopulations there is no need to correct for inter-species variability with Assessment Factors. Separate NOAEL's have been developed for sensitive subpopulations and accommodate intra-species variability that might otherwise require the use of an Assessment factor.
3. NOAEL's derived for different health endpoints are shown in the following table. Those NOAEL's that are the lowest for a given subpopulation are shown in bold text. From this table it can be seen that NOAEL's have been proposed for the most sensitive subsets of the population and define blood lead levels protective against subtle effects. Whereas NOAEL's indexed to endpoints that constitute a material impairment of health might merit consideration of an Assessment Factor greater than "1", the NOAEL's derived in this assessment protect against preclinical effects that precede material health impairment.

Table 14. NOAEL's and proposed blood lead levels for different exposed populations - Pb

Health effects endpoint	NOAEL	Exposed population
Renal system effects	60 µg/dL 25 µg/dL	Adults Child
Haematological effects	50 µg/dL 40 µg/dL	Adults Child
Reproductive effects (male)	45 µg/dL	Male Adults
Nervous system effects (adult)	**40 µg/dL**	**Adults**
Reproductive effects (female)	30 µg/dL	Women of child-bearing capacity
Nervous system effects (child)	**10 µg/dL**	**Individual Child**
Nervous system effects (child)	**5 µg/dL**	**Population Based Child Limit**
Nervous system effects (foetal effects) during pregnancy	**10 µg/dL**	**Pregnant women/women of child-bearing capacity**

4. The most sensitive NOAEL's in adults protect against effects known to be reversible if exposure is reduced.
5. The dose response for lead toxicity is steep and increases the precision with which NOAEL's can be identified. For example, although sub-clinical manifestations of neurotoxicity may be manifested in adults in the range of 40 – 50 µg/dL, significant cognitive impairment would be expected to result from a doubling of blood lead.
6. The effects that are the basis of the NOAEL's applicable to the general population lack functional or clinical significance for the individual and cannot be detected at the level of the individual. Protection is thus being offered against effects which, by many definitions, would not be considered as adverse.
7. In the specific instance of the effect of low-level lead exposure upon IQ development in children, consideration was given to the fact that no threshold has yet to be identified for the effects of lead upon IQ. A NOAEL of 10 µg/dL was set as an exposure level that would not produce adverse effects detectable at the level of the individual. This NOAEL does not preclude potential "societal impacts" resulting from subtle effects of lead upon large numbers of individuals. However, virtually all neurotoxicants are regarded to have a threshold and an "epistemic" threshold was identified for lead (5µg/dL). This level of lead in blood, set as a target for the general population average, would both mitigate against potential societal effects of lead at blood lead levels less than 10µg/dL and guards against exceedance of the NOAEL of 10 µg/dL set to prevent subtle effects detectable at the level of the individual. This tiered

strategy for managing the blood lead levels of children eliminates the need to consider arbitrary Assessment Factors that might be proposed in light of possible population effects of lead at low blood lead levels.

8. Combined, the preceding indicated that the NOAEL's derived here are both conservative and protective of health. The majority of NOAEL's can thus be converted to DNEL's with an Assessment Factor of "1".
9. As assessment factor of 2 will be applied to the NOAEL of 40 µg/dL for adult neurological function since adults in the general population will not be under medical surveillance. Note that, due to non-linearities in the toxicokinetics of lead, an Assessment Factor of 2 is actually equivalent to an approximate five-fold reduction in external exposure.

Separate DNEL's indexed to acute toxicity are not needed. Animal testing indicates that lead is not acutely toxic. Moreover, the DNEL's for repeated dose toxicity are far lower than those that might be considered under acute exposure circumstances.

No DNEL/DMEL has been proposed for mutagenicity. In vitro doses required to produce effects (via what are believed to be indirect, thresholded mechanisms) are far higher than those that possess physiological relevance and in vivo testing via physiologically relevant administration routes is considered to be negative.

DNEL/DMEL has been proposed for cancer. Lead induces tumours (generally of the kidney) via what is believed to be an indirect mechanism that is likely nongenotoxic and a multi-step process involving sustained renal toxicity accompanied by prolonged forced cell proliferation. The generally negative genotoxicity profile of lead is consistent with this rationale, as are the generally negative epidemiology studies of workers occupationally exposed to lead. If kidney cancer were to be induced in humans it would likely proceed via a thresholded non-genotoxic mechanisms that requires exposures higher than those that produce significant renal damage. A DNEL/DMEL for cancer, if derived, would be higher than the NOAEL's that have been derived for neurological function in adults.

The DNEL's derived for different sub-sets of the population in accordance with the preceding are summarised below in terms of lead in blood concentrations.

Table 15. DNEL's Used for General Population Exposure Assessment - Pb

Subpopulation	DNEL	Health Basis of DNEL
Individual Child	10 ug/dL	Impaired cognitive development
Large Population of Children	5 ug/dL	Societal impact of indeterminate nature
Pregnant Woman	10 ug/dL	Developmental toxicity affecting cognitive development
Adult	20 ug/dL	Neuropsychological function

5.0.5 Diantimony trioxide

Table 16. Hazard conclusions for workers – Sb_2O_3

Route	Type of effect	Hazard conclusion	Most sensitive endpoint
Inhalation	Systemic effects - Long-term		
Inhalation	Systemic effects - Acute		
Inhalation	Local effects - Long-term	DNEL (Derived No Effect Level): 0.5 mg/m³	repeated dose toxicity
Inhalation	Local effects - Acute		
Dermal	Systemic effects - Long-term	DNEL (Derived No Effect Level): 281 mg/kg bw/day	repeated dose toxicity
Dermal	Systemic		

Route	Type of effect	Hazard conclusion	Most sensitive endpoint
	effects - Acute		
Dermal	Local effects - Long-term		
Dermal	Local effects - Acute		
Eyes	Local effects	No hazard identified	

Further explanation on hazard conclusions:

- **Inhalation Systemic effects - Long-term:** Not derived, due to lack of systemic toxicity after repeated inhalation exposure in a 12 month toxicity study in rats.

- **Inhalation Systemic effects - Acute:** Not derived, due to lack of acute local toxicity.

- **Inhalation Local effects - Long-term:** Derived, because route of exposure relevant and local effects observed in inhalation toxicity and carcinogenicity studies.

- **Inhalation Local effects - Acute:** Not derived, due to lack of acute local toxicity.

- **Dermal Systemic effects - Long-term:** Derived, because route of exposure relevant for workers.

- **Dermal Systemic effects - Acute:** Not derived, due to lack of acute systemic toxicity.

- **Dermal Local effects - Long-term:** Qualitative approach; irritation potential only relevant under conditions of high chemical dermal exposure and severe sweating.

- **Dermal Local effects - Acute:** Qualitative approach; irritation potential only relevant under conditions of high chemical dermal exposure and severe sweating.

Table 17. Further explanation on DNEL derivation for workers – Sb_2O_3

Route / Type of effect	DNEL derivation	Assessment factors (AF) for DNEL derivation
Inhalation Local effects - Long-term	**Dose descriptor starting point:** NOAEC	
Dermal Systemic effects - Long-term	**Dose descriptor starting point:** NOAEL	**Overall Assessment Factor:** 6

Discussion

Since only local effects in the respiratory tract were seen in animal studies and no systemic effects could be observed, long-term DNELs were derived for local effects only. The same applies for the carcinogenic potential of diantimony trioxide. Because it can be assumed that particle deposition followed by macrophage infiltration, pulmonary inflammation and impaired clearance are pivotal initial steps in the carcinogenic process, diantimony trioxide can be regarded as a threshold carcinogen and thus no DMEL was derived.

Table 18. Hazard conclusions for the general population – Sb_2O_3

Route	Type of effect	Hazard conclusion	Most sensitive endpoint
Inhalation	Systemic effects - Long-term		
Inhalation	Systemic effects - Acute		
Inhalation	Local effects - Long-term	DNEL (Derived No Effect Level): 0.1 mg/m³	repeated dose toxicity
Inhalation	Local effects - Acute		
Dermal	Systemic effects - Long-term	DNEL (Derived No Effect Level): 168.6 mg/kg bw/day	repeated dose toxicity
Dermal	Systemic effects - Acute		
Dermal	Local effects - Long-term		
Dermal	Local effects - Acute		
Oral	Systemic effects - Long-term	DNEL (Derived No Effect Level): 168.6 mg/kg bw/day	repeated dose toxicity
Oral	Systemic effects - Acute		
Eyes	Local effects	No hazard identified	

Further explanation on hazard conclusions:

- **Inhalation Systemic effects - Long-term:** Not derived, due to lack of systemic toxicity after repeated inhalation exposure in a 12 month toxicity study in rats.

- **Inhalation Systemic effects - Acute:** Not derived, due to lack of acute systemic toxicity.

- **Inhalation Local effects - Long-term:** Derived, because route of exposure relevant for consumers and humans exposed via the environment.

- **Inhalation Local effects - Acute:** Not derived, due to lack of acute local toxicity.

- **Dermal Systemic effects - Long-term:** Derived, because route of exposure relevant for consumers and humans exposed via the environment.

- **Dermal Systemic effects - Acute:** Not derived, due to lack of acute systemic toxicity.

- **Dermal Local effects - Long-term:** Not relevant for general population, because irritation potential occurs only under conditions of high chemical dermal exposure and severe sweating.

- **Dermal Local effects - Acute:** Not relevant for general population, because irritation potential occurs only under conditions of high chemical dermal exposure and severe sweating.

- **Oral Systemic effects - Long-term:** Derived, because route of exposure relevant for consumers and humans exposed via the environment.

- **Oral Systemic effects - Acute:** Not derived, due to lack of acute systemic toxicity.

Table 19. Further explanation on DNEL derivation for the general population – Sb_2O_3

Route / Type of effect	DNEL derivation	Assessment factors (AF) for DNEL derivation
Inhalation Local effects - Long-term	**Dose descriptor starting point:** NOAEC	
Dermal Systemic effects - Long-term	**Dose descriptor starting point:** NOAEL	**Overall Assessment Factor:** 10
Oral Systemic effects - Long-term	**Dose descriptor starting point:** NOAEL	**Overall Assessment Factor:** 10

Discussion

Long-term exposure - systemic effects oral DNEL, children = 16.86 mg/kg bw/day (AF=100)

Long-term exposure - systemic effects dermal DNEL, children = 16.86 mg/kg bw/day (AF=100)

Long-term exposure - local effects inhalation DNEL, consumer = 0.1 mg/m³ (AF=5)

Since only local effects in the respiratory tract were seen in animal studies and no systemic effects could be observed, long-term DNELs were derived for local effects only. The same applies for the carcinogenic potential of diantimony trioxide. Because it can be assumed that particle deposition followed by macrophage infiltration, pulmonary inflammation and impaired clearance are pivotal initial steps in the carcinogenic process, diantimony trioxide can be regarded as a threshold carcinogen and thus no DMEL was derived.

5.0.6 Selenium

Table 20. Hazard conclusions for workers - Se

Route	Type of effect	Hazard conclusion	Most sensitive endpoint
Inhalation	Systemic effects - Long-term	DNEL (Derived No Effect Level): 0.05 mg/m³	
Inhalation	Systemic effects - Acute	No hazard identified	
Inhalation	Local effects - Long-term	Hazard unknown (no further information necessary)	
Inhalation	Local effects - Acute	No hazard identified	
Dermal	Systemic effects - Long-term	DNEL (Derived No Effect Level): 7 mg/kg bw/day	
Dermal	Systemic effects - Acute	Hazard unknown (no further information necessary)	
Dermal	Local effects - Long-term	Hazard unknown (no further information necessary)	
Dermal	Local effects -	No hazard identified	

Route	Type of effect	Hazard conclusion	Most sensitive endpoint
	Acute		
Eyes	Local effects	No hazard identified	

Further explanation on hazard conclusions:

- **Inhalation Systemic effects - Long-term:** The rationale for the derivation of the DNEL is laid down in the field "Discussion" below.

- **Inhalation Systemic effects - Acute:** The acute inhalation LC50 in male and female rats for Selenium (fine powder) is greater than 5.67 mg/L, no animal died in an acute inhalation study.

- **Inhalation Local effects - Long-term:** No long-term inhalation studies are available; therefore the long-term local effects cannot be evaluated. However, no signs of irritation were reported in an acute inhalation study and selenium is not classified for eye or skin irritation.

- **Inhalation Local effects - Acute:** The acute inhalation LC50 in male and female rats for Selenium (fine powder) is greater than 5.67 mg/L, no signs of irritation were reported in this acute inhalation study.

- **Dermal Systemic effects - Long-term:** The rationale for the derivation of the DNEL is laid down in the field "Discussion" below.

- **Dermal Systemic effects - Acute:** Acute dermal studies are not available, high peak exposure via dermal route is not expected. Due to the oral LD50 of > 5000 mg/kg bw and the low dermal absorption not potency for acute dermal toxicity is expected for selenium.

- **Dermal Local effects - Long-term:** No long-term dermal studies are available; therefore the long-term local effects cannot be evaluated. However, selenium is not classified for eye or skin irritation.

- **Dermal Local effects - Acute:** No irritation was observed in an in-vitro skin irritation study and an in-vivo eye irritation study with the read-across substance zinc selenite. Selenium is not classified for eye and skin irritation.

- **Eyes Local effects:** No eye irritation was observed in in-vivo eye irritation study with the read-across substance zinc selenite. Selenium is not classified for eye irritation.

Discussion

Rationale for and derivation of DNELs (Derived No Effect Level) for Selenium and its inorganic compounds

Basic approach:

Derivation of DNELs normally starts from the effect data (like the NOAEL: No Observed Adverse Effect Level) gained from appropriate studies with experimental animals and is theoretically calculated for the human situation by application of “standard” assessment (uncertainty) factors to realistically take into account for inter- and intraspecies differences and variability respectively.

In those cases where adequate human data exists, in particular when certain toxicological endpoints may have been observed only in humans but not in experimental animals such human data should be used instead of the animal data as is the case for Selenium and its inorganic compounds, where abundant human data exist and where critical human endpoints have never been observed in the experimental animal.

Further, official toxicological evaluations of those potential health hazards by national and/or international scientific bodies should be followed after having being reviewed critically.

Therefore the human data base will be used for the rationale for and the derivation of DNELs also because Selenium is unique as it is an essential micronutrient for mammalian cells.

Rationale for DNELs:

The rationale for the direct use of human DNELs (for the general population and also for workers) is as follows:

Selenium is an essential element for animals and humans, which is needed for the proper function of a number of enzymes and proteins, like for example for glutathione peroxidases, thioredoxin reductase and deiodase and also binding and transport proteins.

Its "therapeutic" window is narrow, such that Selenium deficiency can cause severe adverse health effects, but also overdosing may lead to the clinical manifestation of Selenosis.

Due to its essentiality human dietary intake of Selenium (from foodstuff and drinking water) is necessary (and also "unavoidable") and has been documented and reviewed with regard to any potential health concerns which may derive from that fact (see below for derivation of DNEL).

Nutritional supplemental Selenium and Selenium added fertilisers are even required in areas with low Selenium concentrations in the soil. Soil which contains 0.02 to 2 mg Selenium/kg is the most important Selenium source for humans (and animals). Since also the amount of Selenium in plants depends on the concentration in soil, diseases of grazing animals have been observed where such levels were low enough {see ref. (1) }.

Due to the facts of essentiality, the "unavoidable" human uptake, the need for nutritional supplementation (in some cases) and the relatively narrow "therapeutic" window accompanied with reliably human effect data national and international scientific bodies have thoroughly evaluated the benefits of Selenium for human health as well as its possible adverse effects.

Therefore in the following for the derivation of DNELs the general population (consumers) and for workers two reviews (besides further supporting documents) will be used mainly, because they are considered to be most relevant due to the facts that they were rather recently published and that they directly address the physiologically necessary oral intake of Selenium (organic and inorganic) for the general population and the due to the exposure of humans (workers) at the workplace respectively:

- European Food Authority (EFSA): SCIENTIFIC OPINION: L-selenomethionine as a source of selenium added for nutritional purposes to food supplements

Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food

Adopted on 14 May 2009, *The EFSA Journal*(2009) 1082, 1-39

available at: http: //www.efsa.europa.eu/en/scdocs/doc/ans_ej1082_L-Selenomethionine_op_en.pdf

- German MAK Commission: Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werten "Selen und seine anorganischen Verbindungen", 1999, 2001 and 2010

available at: http://onlinelibrary.wiley.com/book/10.1002/3527600418

Derivation of DNELs:

In the following a short outline is presented for the derivation of the DNELs for the general population and for workers respectively making use of the above mentioned reviews.

Please note that all DNELs (UL) mentioned below are referring to Selenium; the respective DNELs for the substance to be registered takes into account the Selenium moiety based on the respective molecular weight.

For worker:

Also the German MAK Commission derived its MAK value for the workplace (Threshold Limit Value for Selenium and its inorganic compounds) in 1999 and 2001 from the Yang *et al.* study as mentioned above {see ref. (6), p. 37}.

In 1999 (confirmed in 2001) the MAK value was stated with 0.05 mg/m^{3}equivalentto 7 µg per kg bw per day (for an 8 hour shift) taking into account a lowest relevant NOAEL of 0.15 mg/kg bw per day from a 2-generation study on rats and a LOAEL of < 0.1 mg/kg bw per day from a 4-generation study on mice {see ref. (6): Rosenfeld I and Beath OA (1954): Effect of selenium on reproduction in rats. Proc Soc Exp Biol Med 87: 295—297; Schroeder HA and Mitchener M (1971): Toxic effects of trace elements on the reproduction of mice and rats. Arch Environ

Health 23: 102—106; Schroeder HA, Mitchener M (1972): Selenium and tellurium in mice. Effects on growth, survival, and tumors. Arch Environ Health 24, 66--71}.

Also the MAK value covers all relevant systemic toxicological endpoints (acute toxicity, toxicity after repeated dosing, for reproduction, genotoxicity and carcinogenicity).

For the dermal route the low absoption of 0.1 % has to be taken into account, that means, that the dermal DNEL is set to 7 mg/kg per day.

The registrant(s) noticed the ongoing discussion about effects on diabetes caused by Selenium (see for MAK Commision, 2010: http://onlinelibrary.wiley.com/book/10.1002/3527600418), but due to data from ref. (7) should Selenium have a protective effect against diabetes and there may exist a certain risk that a lowered uptake of Selenium may cause adverse effects on human health.

In particular studies from North America (which caused the suspicion of diabetogenic effects) may overestimate the assumed toxicity of Selenium, because (*citation*)

"…the American and Canadian subjects in this study had higher baseline plasma selenium levels than comparable European subjects. This reflects the fact that the American continent has high levels of selenium in soil and rock, and hence the American population in general has higher dietary intakes of selenium than those in Europe. Serum or plasma selenium levels in European populations without selenium supplementation are in the range of 50-90 ng/mL (Rayman, 2002). In the UK, measurements on approximately 1000 subjects, from the National Diet and Nutrition Surveys of the elderly and of adults and children, showed mean plasma selenium levels of 71 ng/mL (in 1994-5) and 68 ng/mL (in 1997) respectively (Gregory et al., 2000; Bates et al., 2002). These levels may be compared with the mean initial plasma levels of selenium (135 ng/mL) of participants in SELECT, and in the US NPC trial, in which mean initial plasma levels of selenium were 113 ng/mL."{cited fromref. (2), p.23}.

Therefore the overall conclusion is drawn that to date the well defined MAK value of 0.05 mg/m^{3}should be defined the DNEL for the workplace for Selenium and its inorganic compounds.

It is interesting to note that the TLV in the UK for workplace exposure from Selenium and its compounds (except for Hyrogen selenide) for an 8 hour shift is 0.1 mg/m^3{see ref. (8) }.

Final comments:

There is little benefit to be gained from DNELs which define human exposure which is lower than what is thought to be the minimum intake for Selenium necessary to assure for the physiological concentrations in mammalian cells.

For some European regions health relevant Selenium deficiency would occur without the application of Selenium fertilisers or Selenium enriched animal food. Definition of unrealistically low DNELs could therefore establish a potential threat to human health.

The ratio of the DNELs for the general population and for workers is only 1:1.6 (4.3 versus 7 µg/kg bw per day), while the ECHA guidance document R.18 recommends a ratio of 1:2.

This fact indicates for an adequate protection of workers.

References:

(1) Blume*et al*.: Scheffer/Schachtschabel, Lehrbuch der Bodenkunde, Heidelberg, 2010

(2) European Food Safety Authority (EFSA): SCIENTIFIC OPINION: L-selenomethionine as a source of selenium added for nutritional purposes to food supplements, Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food. (Question No EFSA-Q-2005-103, EFSA-Q-2006-195, EFSA-Q-2006-196, EFSA-Q-2006-304), Adopted on 14 May 2009, *The EFSA Journal*(2009) 1082, 1-39

available at: http://www.efsa.europa.eu/en/scdocs/doc/ans_ej1082_L-Selenomethionine_op_en.pdf

(3) Scientific Committee on Food (SCF): Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Selenium (expressed on 19 October 2000): SCF/CS/NUT/UPPLEV/25 Final available at: http://ec.europa.eu/food/fs/sc/scf/out80g_en.pdf

(4) Yang G, Gu L, Zhou R, Yin S (1989) Studies of human maximal and minimal safe intake and requirement of

selenium. In: Wendel A (Hrsg) Selenium in biology and medicine, Springer-Verlag, Berlin, 223—228

(5) Schrauzer GN, 2003: The nutritional significance, metabolism and toxicology of selenomethionine. Adv. Food Nutr. Res. 47, 73-112.

(6) German MAK Commission: Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werten "Selen und seine anorganischen Verbindungen", Freising-Weihenstephan, Germany 1999 - 2010, available at: http://onlinelibrary.wiley.com/book/10.1002/3527600418

(7) Akbaraly TN et al (2010): Plasma selenium and risk of dysglycemia in an elderly French population: results from the prospective Epidemiology of Vascular Ageing Study. Nutrition & Metabolism 2010, 7:21

available at: http://www.nutritionandmetabolism.com/content/7/1/21

(8) Health and Safety Executive: EH40/2005 Workplace exposure limits, Merseyside, UK, 2011 available at: www.hse.gov.uk/

Table 21. Hazard conclusions for the general population - Se

Route	Type of effect	Hazard conclusion	Most sensitive endpoint
Inhalation	Systemic effects - Long-term	DNEL (Derived No Effect Level): 0.015 mg/m³	
Inhalation	Systemic effects - Acute	No hazard identified	
Inhalation	Local effects - Long-term	Hazard unknown (no further information necessary)	
Inhalation	Local effects - Acute	No hazard identified	
Dermal	Systemic effects - Long-term	DNEL (Derived No Effect Level): 4.3 mg/kg bw/day	
Dermal	Systemic effects - Acute	Hazard unknown (no further information necessary)	
Dermal	Local effects - Long-term	Hazard unknown (no further information necessary)	
Dermal	Local effects - Acute	No hazard identified	
Oral	Systemic effects - Long-term	DNEL (Derived No Effect Level): 4.3 µg/kg bw/day	
Oral	Systemic effects - Acute	No hazard identified	
Eyes	Local effects	No hazard identified	

Further explanation on hazard conclusions:

- **Inhalation Systemic effects - Long-term:** The rationale for the derivation of the DNEL is laid down in the field "Discussion" below.

- **Inhalation Systemic effects - Acute:** The acute inhalation LC50 in male and female rats for Selenium (fine powder) is greater than 5.67 mg/L, no animal died in an acute inhalation study.

- **Inhalation Local effects - Long-term:** No long-term inhalation studies are available; therefore the long-term local effects cannot be evaluated. However, no signs of irritation were reported in an acute inhalation study and selenium is not classified for eye or skin irritation.

- **Inhalation Local effects - Acute:** The acute inhalation LC50 in male and female rats for Selenium (fine powder) is greater than 5.67 mg/L, no signs of irritation were reported in this acute inhalation study.

- **Dermal Systemic effects - Long-term:** The rationale for the derivation of the DNEL is laid down in the field "Discussion" below.

- **Dermal Systemic effects - Acute:** Acute dermal studies are not available, high peak exposure via dermal route is not expected. Due to the oral LD50 of > 5000 mg/kg bw and the low dermal absorption not potency for acute dermal toxicity is expected for selenium.

- **Dermal Local effects - Long-term:** No long-term dermal studies are available; therefore the long-term local effects cannot be evaluated. However, selenium is not classified for eye or skin irritation.

- **Dermal Local effects - Acute:** No irritation was observed in an in-vitro skin irritation study and an in-vivo eye irritation study with the read-across substance zinc selenite. Selenium is not classified for eye and skin irritation.

- **Oral Systemic effects - Long-term:** The rationale for the derivation of the DNEL is laid down in the field "Discussion" below.

- **Oral Systemic effects - Acute:** The acute oral LD50 of selenium is > 5000 mg/kg bw. No animal died in two studies conducted with either selenium powder or crude selenium.

- **Eyes Local effects:** No eye irritation was observed in in-vivo eye irritation study with the read-across substance zinc selenite. Selenium is not classified for eye irritation.

Discussion

Rationale for and derivation of DNELs (Derived No Effect Level) for Selenium and its inorganic compounds

Basic approach:

Derivation of DNELs normally starts from the effect data (like the NOAEL: No Observed Adverse Effect Level) gained from appropriate studies with experimental animals and is theoretically calculated for the human situation by application of “standard” assessment (uncertainty) factors to realistically take into account for inter- and intraspecies differences and variability respectively.

In those cases where adequate human data exists, in particular when certain toxicological endpoints may have been observed only in humans but not in experimental animals such human data should be used instead of the animal data as is the case for Selenium and its inorganic compounds, where abundant human data exist and where critical human endpoints have never been observed in the experimental animal.

Further, official toxicological evaluations of those potential health hazards by national and/or international scientific bodies should be followed after having being reviewed critically.

Therefore the human data base will be used for the rationale for and the derivation of DNELs also because Selenium is unique as it is an essential micronutrient for mammalian cells.

Rationale for DNELs:

The rationale for the direct use of human DNELs (for the general population and also for workers) is as follows:

Selenium is an essential element for animals and humans, which is needed for the proper function of a number of enzymes and proteins, like for example for glutathione peroxidases, thioredoxin reductase and deiodase and also binding and transport proteins.

Its “therapeutic” window is narrow, such that Selenium deficiency can cause severe adverse health effects, but also overdosing may lead to the clinical manifestation of Selenosis.

Due to its essentiality human dietary intake of Selenium (from foodstuff and drinking water) is necessary (and also “unavoidable”) and has been documented and reviewed with regard to any potential health concerns which may derive from that fact (see below for derivation of DNEL).

Nutritional supplemental Selenium and Selenium added fertilisers are even required in areas with low Selenium concentrations in the soil. Soil which contains 0.02 to 2 mg Selenium/kg is the most important Selenium source for humans (and animals). Since also the amount of Selenium in plants depends on the concentration in soil, diseases of grazing animals have been observed where such levels were low enough {see ref. (1) }.

Due to the facts of essentiality, the “unavoidable” human uptake, the need for nutritional supplementation (in some cases) and the relatively narrow “therapeutic” window accompanied with reliably human effect data national and international scientific bodies have thoroughly evaluated the benefits of Selenium for human health as well as its possible adverse effects.

Therefore in the following for the derivation of DNELs the general population (consumers) and for workers two reviews (besides further supporting documents) will be used mainly, because they are considered to be most relevant due to the facts that they were rather recently published and that they directly address the physiologically necessary oral intake of Selenium (organic and inorganic) for the general population and the due to the exposure of humans (workers) at the workplace respectively:

- European Food Authority (EFSA): SCIENTIFIC OPINION: L-selenomethionine as a source of selenium added for nutritional purposes to food supplements

Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food

Adopted on 14 May 2009, *The EFSA Journal*(2009) 1082, 1-39

available at: http: //www.efsa.europa.eu/en/scdocs/doc/ans_ej1082_L-Selenomethionine_op_en.pdf

- German MAK Commission: Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werten “Selen und seine anorganischen Verbindungen”, 1999, 2001 and 2010

available at: http://onlinelibrary.wiley.com/book/10.1002/3527600418

Derivation of DNELs:

In the following a short outline is presented for the derivation of the DNELs for the general population and for workers respectively making use of the above mentioned reviews.

Please note that all DNELs (UL) mentioned below are referring to Selenium; the respective DNELs for the substance to be registered takes into account the Selenium moiety based on the respective molecular weight.

For general population:

EFSA and its panel stated, that (*citation*) “*the toxicity of L-selenomethionine is comparable with other forms of selenium”* {see ref. (2), p. 2}. This is particularly proven by the facts that bioavailability of L-Selenomethionine is higher than for inorganic Selenium compounds, that the biological half-live is also longer for L-Selenomethionine and that all Selenium moieties after systemic uptake are reduced to the Selenid anion (Se^{2-}) which represents the “starting point” for its mode of action an further metabolic fate.

From this follows, that the assessment as laid down by the EFSA panel for L-selenomethionine as a nutritional supplement is also valid for the inorganic Selenium compounds to be registered and the EFSA panel`s derivation of a Tolerable Upper Intake Level (UL) can be used accordingly without any further modification and therefore represents the human DNEL for the oral route.

The EFSA panel also confirms the UL, which was set by the Scientific Committee on Food (SCF) for inorganic Selenium compounds, to be 300 µg Selenium per person per day (equivalent to 4.3 µg per kg bodyweight (bw) per day for a person of 70 kg) {see ref. (3) }.

The starting point here was a NOAEL from (epidemiological) human studies of 850 µg per person per day or 12 µg/kg bw per day for clinical selenosis. This figure was published by Yang *et al.* {see ref. (4) }. and was derived

from observations on Chinese subjects living in seleniferous areas. It results from an increasing effect on prothombine time by higher Selenium levels. The SCF applied an additional assessment factor of 3, because the NOAEL was derived from data for a lifetime uptake for all subgroups of a population. This approach is in line with ECHA recommendations.

It has to emphasized, that the study of Yang et. al. is not under dispute with respect to its reliability and represents a common denominator of the reviewed papers.

Further assessment factors for inter- or intraspecies variability or for time scaling are not required for such epidemiological data.

This human NOAEL is far below the most relevant NOAEL for inorganic Selenium compounds of 0.12 mg/kg bw per day from animal studies by far, which was identified by the EFSA panel from a 90-day study on dogs {see ref. (2) p.17, referring to ref. (5) }.

The EFSA panel considers, that overall (*citation*) *„the toxicity of L-selenomethionine is comparable to other forms of selenium, in terms of equivalent amounts of bioavailable selenium. As with other selenium compounds, the results of toxicological studies with L-selenomethionine in animals are indicative of a steep dose-response curve, with a threshold for onset of toxicity in the range of 100–400 µg selenium/kg bw/day, dependent on the species. "*{cited from ref. (2), p. 25}

This statement includes all relevant systemic toxicological endpoints (acute toxicity, toxicity after repeated dosing, for reproduction, genotoxicity and carcinogenicity) without restriction.

The derived human NOAEL (equivalent to the DNEL) seems to cover the general population for all routes of exposure; it is 300 µg Selenium per person per day or 4.3 µg/kg bw per day which represents the UL of the EFSA panel and the SCF.

Basically this UL was very recently fully acknowledged by the Office of Dietary Supplements of the US National Institutes of Health (available at: http://ods.od.nih.gov/factsheets/Selenium-HealthProfessional/).

Similarly in a document from the World Health Organization (WHO) for drinking water quality {see ref. (6) } the human NOAEL for Selenium uptake was stated to be 4 µg/kg bw per day.

Finally the US Environmental Protection Agency has defined a Reference Dose (RfD) for Selenium to be 5 µg/kg bw per day (available at: http://www.epa.gov/iris/subst/0472.htm).

The derived DNEL of 300 µg Selenium per person per day or 4.3 µg/kg bw per day will therefore be used for the oral and dermal route.

The corresponding DNEL for inhalation expressed as concentration in the air is calculated by:

Daily respiratory volume = 20 m^3 according to ECHA guidance R.8 for 24 hours of exposure.

DNEL = 300 µg per person per day,

$DNEL_{inh}$= 0.3 mg/20 m^3= 0.015 mg/m^3or 15 µg/m^3

References:

(1) Blume *et al.*: Scheffer/Schachtschabel, Lehrbuch der Bodenkunde, Heidelberg, 2010

(2) European Food Safety Authority (EFSA): SCIENTIFIC OPINION: L-selenomethionine as a source of selenium added for nutritional purposes to food supplements, Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food. (Question No EFSA-Q-2005-103, EFSA-Q-2006-195, EFSA-Q-2006-196, EFSA-Q-2006-304), Adopted on 14 May 2009, *The EFSA Journal*(2009) 1082, 1-39

available at: http://www.efsa.europa.eu/en/scdocs/doc/ans_ej1082_L-Selenomethionine_op_en.pdf

(3) Scientific Committee on Food (SCF): Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Selenium (expressed on 19 October 2000): SCF/CS/NUT/UPPLEV/25 Final

available at: http://ec.europa.eu/food/fs/sc/scf/out80g_en.pdf

(4) Yang G, Gu L, Zhou R, Yin S (1989) Studies of human maximal and minimal safe intake and requirement of selenium. In: Wendel A (Hrsg) Selenium in biology and medicine, Springer-Verlag, Berlin, 223—228

(5) Schrauzer GN, 2003: The nutritional significance, metabolism and toxicology of selenomethionine. Adv. Food Nutr. Res. 47, 73-112.

(6) German MAK Commission: Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werten "Selen und seine anorganischen Verbindungen", Freising-Weihenstephan, Germany 1999 - 2010, available at: http://onlinelibrary.wiley. com/book/10.1002/3527600418

(7) Akbaraly TN et al (2010): Plasma selenium and risk of dysglycemia in an elderly French population: results from the prospective Epidemiology of Vascular Ageing Study. Nutrition & Metabolism 2010, 7:21

available at: http://www.nutritionandmetabolism.com/content/7/1/21

(8) Health and Safety Executive: EH40/2005 Workplace exposure limits, Merseyside, UK, 2011 available at: www.hse.gov.uk/

5.0.7 Tellurium

Table 22. Hazard conclusions for workers - Te

Route	Type of effect	Hazard conclusion	Most sensitive endpoint
Inhalation	Systemic effects - Long-term	Insufficient data available (further information necessary)	
Inhalation	Systemic effects - Acute	Low hazard (no threshold derived)	
Inhalation	Local effects - Long-term	Hazard unknown (no further information necessary)	
Inhalation	Local effects - Acute	No hazard identified	
Dermal	Systemic effects - Long-term	Insufficient data available (further information necessary)	
Dermal	Systemic effects - Acute	Hazard unknown (no further information necessary)	
Dermal	Local effects - Long-term	Hazard unknown (no further information necessary)	
Dermal	Local effects - Acute	No hazard identified	
Eyes	Local effects	No hazard identified	

Further explanation on hazard conclusions:

- **Inhalation Systemic effects - Long-term:** A repeated dose toxicity study according to OECD Guideline 407 (Repeated Dose 28-Day Oral Toxicity in Rodents) and a screening study according to OECD Guideline 421 (Reproduction / Developmental Toxicity Screening Test) with tellurium dioxide were commissioned to CiToxLAB, 8200 Veszprem, Hungary. Even though repeatedly requested, no draft report was available for evaluation until mid of April 2013. Read-across from the data generated from these studies is planned; therefore the tellurium dossier is incomplete with regard to these toxicological endpoints. Consequently derivation of DNELs is not possible. An update will be conducted as soon as the data are available, including the respective inhalation DNELs, derived by route-to-route extrapolation.

- **Inhalation Systemic effects - Acute:** Based on the LC50 tellurium of > 2.42 mg/L the low hazard category is assigned.

- **Inhalation Local effects - Long-term:** No long-term studies are available for the inhalation route; therefore long-term local effects cannot be evaluated. For systemic effects DNEL will be derived by route-to-route extrapolation.

- **Inhalation Local effects - Acute:** In an acute inhalation toxicity study according to OECD guideline 403 with tellurium, greyish, brownish or black stained lungs were seen in all rats at autopsy. However, irritating or inflammatory effects are not reported.

- **Dermal Systemic effects - Long-term:** A repeated dose toxicity study according to OECD Guideline 407 (Repeated Dose 28-Day Oral Toxicity in Rodents) and a screening study according to OECD Guideline 421 (Reproduction / Developmental Toxicity Screening Test) with tellurium dioxide were commissioned to CiToxLAB, 8200 Veszprem, Hungary. Even though repeatedly requested, no draft report was available for evaluation until mid of April 2013. Read-across from the data generated from these studies is planned; therefore the tellurium dossier is incomplete with regard to these toxicological endpoints. Consequently derivation of DNELs is not possible. An update will be conducted as soon as the data are available, including the respective dermal DNELs, derived by route-to-route extrapolation.

- **Dermal Systemic effects - Acute:** Acute dermal studies are not available, high peak exposure via dermal route is not expected.

- **Dermal Local effects - Long-term:** No long-term dermal studies are available; therefore the long-term local effects cannot be evaluated. However, tellurium is not classified for eye or skin irritation.

- **Dermal Local effects - Acute:** No irritation was observed in in-vitro skin and eye irritation studies with tellurium. Tellurium is not classified for eye and skin irritation.

- **Eyes Local effects:** No irritation was observed in in-vitro skin and eye irritation studies with tellurium. Tellurium is not classified for eye and skin irritation.

Table 23. Hazard conclusions for the general population - Te

Route	Type of effect	Hazard conclusion	Most sensitive endpoint
Inhalation	Systemic effects - Long-term	Insufficient data available (further information necessary)	
Inhalation	Systemic effects - Acute	Low hazard (no threshold derived)	
Inhalation	Local effects - Long-term	Hazard unknown (no further information necessary)	
Inhalation	Local effects - Acute	No hazard identified	
Dermal	Systemic effects - Long-term	Insufficient data available (further information necessary)	
Dermal	Systemic effects - Acute	Hazard unknown (no further information necessary)	
Dermal	Local effects - Long-term	Hazard unknown (no further information necessary)	
Dermal	Local effects - Acute	No hazard identified	
Oral	Systemic effects - Long-	Insufficient data available (further information necessary)	

Route	Type of effect	Hazard conclusion	Most sensitive endpoint
	term		
Oral	Systemic effects - Acute	No hazard identified	
Eyes	Local effects	No hazard identified	

Further explanation on hazard conclusions:

- **Inhalation Systemic effects - Long-term:** A repeated dose toxicity study according to OECD Guideline 407 (Repeated Dose 28-Day Oral Toxicity in Rodents) and a screening study according to OECD Guideline 421 (Reproduction / Developmental Toxicity Screening Test) with tellurium dioxide were commissioned to CiToxLAB, 8200 Veszprem, Hungary. Even though repeatedly requested, no draft report was available for evaluation until mid of April 2013. Read-across from the data generated from these studies is planned; therefore the tellurium dossier is incomplete with regard to these toxicological endpoints. Consequently derivation of DNELs is not possible. An update will be conducted as soon as the data are available, including the respective inhalation DNELs, derived by route-to-route extrapolation.

- **Inhalation Systemic effects - Acute:** Based on the LC50 tellurium of > 2.42 mg/L the low hazard category is assigned.

- **Inhalation Local effects - Long-term:** No long-term studies are available for the inhalation route; therefore long-term local effects cannot be evaluated. For systemic effects DNEL will be derived by route-to-route extrapolation.

- **Inhalation Local effects - Acute:** In an acute inhalation toxicity study according to OECD guideline 403 with tellurium, greyish, brownish or black stained lungs were seen in all rats at autopsy. However, irritating or inflammatory effects are not reported.

- **Dermal Systemic effects - Long-term:** A repeated dose toxicity study according to OECD Guideline 407 (Repeated Dose 28-Day Oral Toxicity in Rodents) and a screening study according to OECD Guideline 421 (Reproduction / Developmental Toxicity Screening Test) with tellurium dioxide were commissioned to CiToxLAB, 8200 Veszprem, Hungary. Even though repeatedly requested, no draft report was available for evaluation until mid of April 2013. Read-across from the data generated from these studies is planned; therefore the tellurium dossier is incomplete with regard to these toxicological endpoints. Consequently derivation of DNELs is not possible. An update will be conducted as soon as the data are available, including the respective dermal DNELs, derived by route-to-route extrapolation.

- **Dermal Systemic effects - Acute:** Acute dermal studies are not available, high peak exposure via dermal route is not expected.

- **Dermal Local effects - Long-term:** No long-term dermal studies are available; therefore the long-term local effects cannot be evaluated. However, tellurium is not classified for eye or skin irritation.

- **Dermal Local effects - Acute:** No irritation was observed in in-vitro skin and eye irritation studies with tellurium. Tellurium is not classified for eye and skin irritation.

- **Oral Systemic effects - Long-term:** A repeated dose toxicity study according to OECD Guideline 407 (Repeated Dose 28-Day Oral Toxicity in Rodents) and a screening study according to OECD Guideline 421 (Reproduction / Developmental Toxicity Screening Test) with tellurium dioxide were commissioned to CiToxLAB, 8200 Veszprem, Hungary. Even though repeatedly requested, no draft report was available for evaluation until mid of April 2013. Read-across from the data generated from these studies is planned; therefore the tellurium dossier is incomplete with regard to these toxicological endpoints. Consequently derivation of DNELs is not possible. An update will be conducted as soon as the data are available, including the respective oral DNELs.

- **Oral Systemic effects - Acute:** The acute oral LD50 of tellurium is > 5000 mg/kg bw. No animal died in a total of three studies conducted with rats and mice.

- **Eyes Local effects:** No irritation was observed in in-vitro skin and eye irritation studies with tellurium. Tellurium is not classified for eye and skin irritation.