RISK ASSESSMENT REPORT

ZINC CHLORIDE

CAS-No.: 7646-85-7

EINECS-No.: 231-592-0

GENERAL NOTE

This document contains:

RISK ASSESSMENT

ZINC CHLORIDE

CAS-No.: 7646-85-7

EINECS-No.: 231-592-0

Final report, May 2008

PART 1

Environment

Rapporteur for the risk evaluation of zinc chloride is the Ministry of Housing, Spatial Planning and the Environment (VROM) in consultation with the Ministry of Social Affairs and Employment (SZW) and the Ministry of Public Health, Welfare and Sport (VWS). Responsible for the risk evaluation and subsequently for the contents of this report is the rapporteur.

The scientific work on this report has been prepared by the Netherlands Organization for Applied Scientific Research (TNO) and the National Institute of Public Health and Environment (RIVM), by order of the rapporteur.

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PREFACE

For zinc metal (CAS No. 7440-66-6), zinc distearate (CAS No. 557-05-1 / 91051-01-3), zinc oxide (CAS No.1314-13-2), zinc chloride (CAS No.7646-85-7), zinc sulphate (CAS No.7733-02-0) and trizinc bis(orthophosphate) (CAS No.7779-90-0) risk assessments were carried out within the framework of EU Existing Chemicals Regulation 793/93. For each compound a separate report has been prepared. It should be noted, however, that the risk assessment on zinc metal contains specific sections (as well in the exposure part as in the effect part) that are relevant for the other zinc compounds as well. For these aspects, the reader is referred to the risk assessment report on zinc.

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OVERALL CONCLUSIONS/RESULTS OF THE RISK ASSESSMENT

CAS No. 7646-85-7

EINECS No. 231-592-0

IUPAC Name Zinc chloride

( ) i) There is need for further information and/or testing

(X) ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already

(X) iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account

(X) iii*) A conclusion applied to local scenarios in which the local scenario merits conclusion (ii) but where (possibly) due to high regional background concentrations a local risk cannot be excluded.

LOCAL

Conclusion (ii) is drawn for all local scenarios, including secondary poisoning, except those listed below.

Conclusion **iii) or iii*)** is drawn for the specified scenarios, because:

STP

- the PEC_{STP} exceeds the $PNEC_{add}$ for microorganisms at a number of production sites and processing scenarios listed in Table 3.4.11 (**conclusion iii**).

Surface water

- for one production site and two processing scenarios listed in Table 3.4.11 the $Clocal_{add}$ / $PNEC_{add}$ ratio is > 1 (**conclusion iii**). For one production site listed in Table 3.4.11 the $Clocal_{add}$ / $PNEC_{add}$ ratio falls between 0.5 and 1, which indicates that a potential risk at local scale cannot be excluded due to the possible existence of high regional background concentrations (**conclusion iii***).

Sediment

- for three production sites and four processing scenarios listed in Table 3.4.11 the $Clocal_{add}$ in sediment exceeds the $PNEC_{add}$ in sediment (**conclusion iii**). All remaining sites and scenarios listed in Table 3.4.11 have a **conclusion iii*)** for sediment because a potential risk at the local scale cannot be excluded due to the possible existence of high regional background concentrations.

Soil

- three processing scenarios listed in Table 3.4.11 resulted in PEC_{add} / $PNEC_{add}$ ratios >1 for the terrestrial compartment (**conclusion iii**).

REGIONAL

The regional risk characterisation is discussed in the RAR on Zinc Metal.

1 GENERAL SUBSTANCE INFORMATION

Identification of the substance

CAS-No.	7646-85-7
EINECS-No.	231-592-0
IUPAC name	Zinc chloride
Synonyms	Zinc dichloride, zinc(II)chloride, zinc butter, butter of zinc
Molecular formula	$ZnCl_2$
Structural formula	$ZnCl_2$
Molecular weight	136.27

Purity/impurities, additives

Purity	Liquid = 57.7% w/w Solid > 96% w/w
Impurity	Claimed confidential
Additives	none

Physico-chemical properties

In table 1A the physico-chemical properties of zinc chloride are summarized.

Table 1A Physico-chemical properties of zinc chloride

Property	Result	Comment
Physical state	solid, crystalline	*
Melting point	283 ºC	*
Boiling point	732 ºC	*
Relative density	2.91	*
Vapour pressure	1.33 hPa at 428 ºC	*
Surface tension	no data	***
Water solubility	4320 g/l at 25 ºC	*
Solubility in other solvents	1000g/l ethanol; soluble in acetone; low solubility in diethylether; unsoluble in ammonia	*
Partition coefficient n-octanol/water (log value)	no data	***
Flash point	not applicable	**
Flammability	not flammable	**
Autoflammability temperature	not-autoflammable	**
Explosive properties	not explosive	**
Oxidizing properties	not oxidizing	**

* More than one apparently independent source. No methods are specified.

** Conclusion based on theoretical and/or structural considerations.

*** Acceptable on theoretical and/or structural considerations.

These data are mainly derived from CRC Handbook of Chemistry and Physics (1995), Sax's Dangerous Properties of Industrial Materials (1984), Patty's Industrial Hygiene and Toxicology (1981), Römpp Chemie Lexikon (1995), and Ullmann's Encyklopädie der Technischen Chemie (1983). For an extended description see HEDSET.

Conclusion:
Data on surface tension and partition coefficient were not provided. In view of the nature of the substance, determination of these parameters is considered to be irrelevant (dissociation). Information on flammability, explosive properties and oxidizing properties is not available. However, on theoretical considerations the compound is concluded to be not flammable, not explosive and not oxidizing. All other required physico-chemical data were submitted. None of these data is based on test results, substantiated with reports. However, the data are considered as sufficiently reliable to fulfil the Annex VIIA requirements.

Classification and labelling (human health, environment and physico-chemical)

Annex 1 of Directive 67/548/EEC contains a list of harmonised classifications and labellings for substances or groups of substances, which are legally binding within the EU.
For zinc chloride the current Annex 1 classification and labelling (29th ATP, 2004) is as follows:

Classification
Xn; R22
C; R34
N; R50-53

Labelling
C; N
R: 22-34-50/53
S: (1/2-)26-36/37/39-45-60-61

Specific concentration limits

Concentration	*Classification*
C ≥ 25%	C, N; R22-34-50/53
10% ≤ C < 25%	C, N; R34-51/53
5% ≤ C < 10%	Xn, N; R36/37/38-51/53
2.5% ≤ C < 5%	N; R51/53
0.25% ≤ C < 2.5%	R52/53

2 GENERAL INFORMATION ON EXPOSURE

2.1 PRODUCTION

The zinc chloride production sites in the European Union with a volume of more than 1000 t/y are presented in Table 2.1.1.

Table 2.1.1 Production sites of zinc chloride (>1000 t/y) in the EU (Information from industry)

Company	**Location**
Floridienne Chimie S.A.	Ath, Belgium
Produits Chimiques de Loos	Loos, France
Th. Goldschmidt AG	Mannheim, Germany
S.A. Lipmes	Manresa, Spain
William Blythe Ltd.	Accrington, Lancashire, UK

The total production volume of zinc chloride in the EU is about 28,600 t/y, based on the values presented in Table 3.2.1, page 16. The submitted exported volume of zinc chloride for the EU is about 11,600 t/y. Zinc chloride is not imported in the EU.

2.1.1 Production process

Zinc chloride is mainly produced by treatment of secondary raw material. The production process is dependent on the used raw material. In case of liquid zinc containing raw material, zinc chloride is produced by purifying and cleaning the hydrochloric acid fluid. In case of solid zinc containing raw material, the solids are first dissolved in a hydrochloric acid fluid, before it is purified and cleaned. During the production process, sludges primarily containing either lead or other heavy metals (copper, cadmium) are precipitated and separated, which in return represents secondary raw materials. The cleaned zinc chloride fluids are marketed as fluids or as solid zinc chloride crystals as such, or in combination with other inorganic salts like ammonium chloride. The wastes produced are sludges consisting largely of iron hydroxide, containing residual zinc as hydroxide.

2.2 USE PATTERN

Table 2.2.1 shows the industrial and use categories of zinc chloride. Zinc chloride is mainly used in the EU in the chemical industry (37%), galvanising industry (28%), battery industry (15%), agrochemical industry (fungicides) (13%) and in the printing and dye industry (7%) (information from industry). The quantitative estimates, mentioned between brackets, are from the year 1994. The main type of use category of zinc chloride can be characterised as non dispersive use.

Table 2.2.1 Industrial and use categories of zinc chloride in the EU

Industrial category	**EC no.**	**Use category**	**EC no**
Agrochemical industry	3	Intermediate for pesticides (fungicide) production	33
Chemical industry: basic chemicals	2	Process regulators Pharmaceuticals Others: catalyst in synthesis of vitamins	43 41 55
Electrical/electronic engineering industry	4	Conductive agents	12
Metal extraction, refining and processing industry	8	Electroplating agents Flux agents for casting Welding and soldering agents	17 24 54
Textile processing industry	13	Others: part of cationic dyes	55
Paints, lacquers and varnishes industry	14	Others: part of inks	55

3 ENVIRONMENT

3.1 GENERAL INTRODUCTION

The presence of zinc in the environment due to natural processes (resulting in a natural background concentration of zinc in all environmental compartments, incl. organisms), the chemical processes that will affect the speciation of zinc in the environment, and the fact that zinc is an essential element have implications for the environmental exposure and effect assessment of zinc and thus for the risk characterisation of zinc.

Since the Technical Guidance Document (TGD) does not provide detailed information on how to deal with (essential) elements that have a natural background concentration in the environment, such as zinc, the "added risk approach" (according to Struijs et al., 1997 and Crommentuijn et al., 1997) has been used in this risk assessment report on zinc. In this approach both the "Predicted Environmental Concentration"(PEC) and the "Predicted No Effect Concentration" (PNEC) are determined on the basis of the added amount of zinc, resulting in an "*added* Predicted Environmental Concentration" (PEC_{add}) and "*added* Predicted No Effect Concentration" ($PNEC_{add}$), respectively. The use of the added risk approach (a method that in principle can be used for all naturally occurring substances) implies that only the anthropogenic amount of a substance, i.e. the amount added to the natural background concentration, is considered to be relevant for the effect assessment of that substance. Thus, a possible contribution of the natural background concentration to toxic effects is ignored.

In the present environmental exposure assessment (section 3.2), the use of the added risk approach implies that the PEC_{add} values have been calculated from zinc emissions due to anthropogenic activities. Thus, the PEC_{add} is the anthropogenic part of the zinc concentration in the environment. By focusing only on the anthropogenic part of zinc, the problem of the great variety of natural background concentrations of zinc over the different geographic regions is eliminated. Of course it is realised that comparison of the PEC_{add} with measured environmental concentrations must take into account that the latter values comprise the natural background concentration (Cb) and the anthropogenic part.

In the environmental effect assessment (section 3.3), the use of the added risk approach implies that the $PNEC_{add}$ has been derived from toxicity data that are based on the added zinc concentration in the tests. Thus, the $PNEC_{add}$ is the maximum permissible addition to the background concentration. From the background concentration (Cb) and the $PNEC_{add}$, the PNEC can be calculated: $PNEC = Cb + PNEC_{add}$.

Finally, in the environmental risk characterisation (section 3.4), the use of the added risk approach implies the evaluation of the PEC_{add} / $PNEC_{add}$ ratios. In case measured environmental concentrations are used in the risk characterisation, either the background concentration has to be subtracted from the measured environmental concentration (resulting in a "PEC_{add} / $PNEC_{add}$" ratio) or the background concentration has to be added to the $PNEC_{add}$ (resulting in a traditional "PEC / PNEC" ratio).

3.2 EXPOSURE ASSESSMENT

General information about zinc is available in many publications, e.g. the 'Integrated Criteria Document Zinc' (Cleven et al., 1993) and in the 'Environmental Health Criteria for Zinc' (WHO, 1996). In the present series of zinc risk assessment reports only a summary of the available information is given. In the sections 3.2.2, 3.2.3 and 3.2.4 of the zinc metal RAR, general characteristics are described which are relevant for the release and fate of zinc in the environment. It must be noted that it is very difficult to define the exact form of zinc once emitted by the zinc chloride industry. Hence, for pragmatically reasons in this document emissions and environmental concentrations are expressed as zinc and not as e.g. zinc chloride, unless otherwise mentioned.

Section 3.2.1 presents the added Predicted Environmental Concentrations ((PE)C_{add}s) for several exposure scenarios. The (PE)C_{add}s are derived from either modelling or measured exposure data. The local exposure assessment for the production and use of zinc chloride is presented in section 3.2.1.2. This local exposure assessment is focused on the emissions of industrial point sources. A regional exposure assessment is described in section 3.2.5.3 (zinc metal RAR). The regional exposure assessment includes the industrial and diffuse emissions of all current EU priority zinc compounds. In case of diffuse emissions it is not possible to distinguish between emissions from current EU priority zinc compounds and non-EU priority list zinc compounds. The diffuse emissions may thus also comprise emissions from other zinc compounds (Figure 3.2.1) For the local exposure assessment of the other zinc compounds the reader is referred to those separate reports.

A general description about the release and fate of zinc (sections 3.2.2, 3.2.3 and 3.2.4) and the regional exposure assessment (section 3.2.5.3) is only presented in the zinc metal report, but it is applicable to the exposure assessment of all current EU priority zinc compounds.

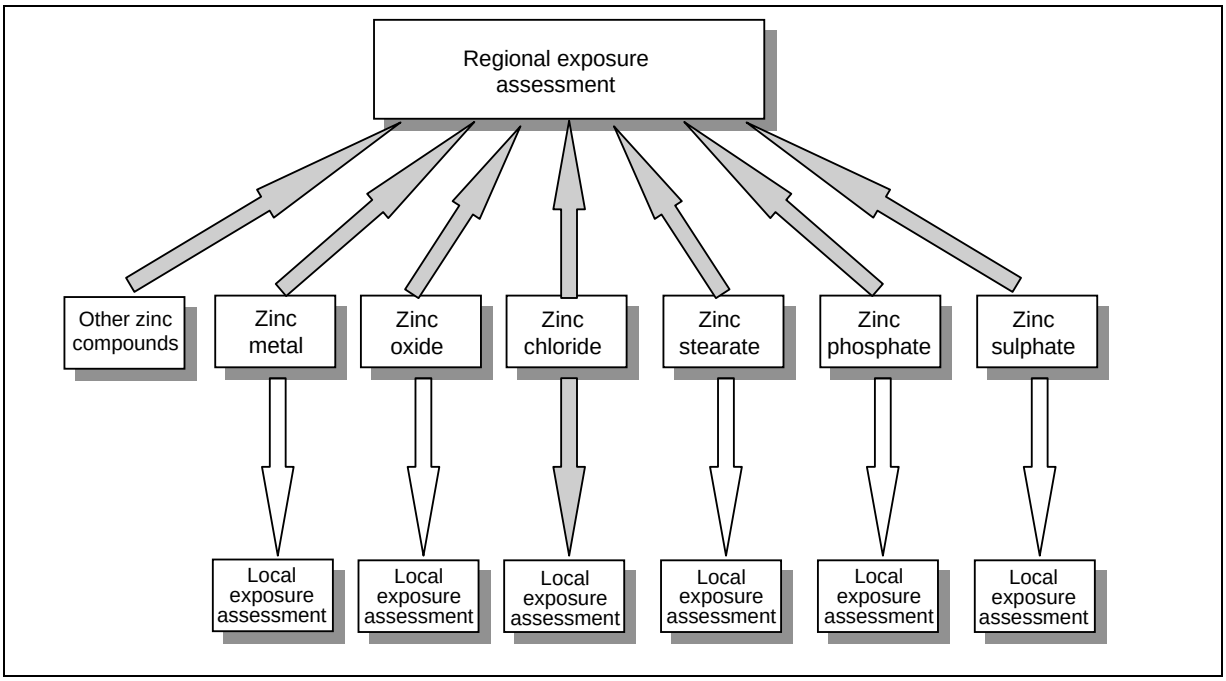

Figure 3.2.1 Theoretical outline for the regional and local exposure assessment for zinc chloride (and other zinc compounds).

3.2.1 Exposure scenarios

3.2.1.1 General

The objective of this exposure assessment is to determine the emissions, pathways and rates of movement and the transformation of zinc chloride in order to estimate the added predicted environmental concentration ((PE)C) for the different environmental compartments. The EU-Technical Guidance document (TGD, 1996) and the European Union System for the Evaluation of Substances (EUSES 1.0) are used as a guideline to achieve this objective. The entry for estimating the environmental concentrations is, when available, the submitted information from industry, including monitoring data, and/or information gathered from other sources. Deviations from the TGD are mentioned in the text. Otherwise (PE)C values will be calculated according to the TGD. For modelling the behaviour of zinc in the environment the octanol-water partitioning coefficient (Kow) and the water solubility are not appropriate. Measured Kp values are used instead for soil, sediment and suspended matter (TGD (Ap. VIII), 1996). See sections 3.2.2 and 3.2.3 (zinc metal report) for more information about the used Kp values. The vapour pressure has been fixed on a low value of 1.10^{-10} Pa and the biotic and abiotic degradation rates have been minimised (TGD (Ap. VIII), 1996).

In the local exposure assessment the agricultural soil concentrations are calculated accounting for accumulation for 10 consecutive years. One should realise that this TGD defined period of 10 years is of lesser relevance to metals than to most organic chemicals. For zinc no steady state will be reached within 10 years. Unless stated otherwise, the input sources to the agricultural soil compartments are the usage of sludge and the airborne deposition. For zinc the only removal or output from the agricultural soil compartment is by leaching to deeper soil layers. It is emphasised that other input or output sources, e.g. the use of manure or the crop offtake, are not taken into account for zinc in the local scenarios. In the regional exposure assessment steady state agricultural soil concentration are calculated, accounting for the input sources deposition from air, sludge application, corrosion, manure and fertilisers and the output sources leaching to deeper soil layers and offtake via crops. The reason that factors like manure input and removal via crops have been applied in the regional calculations and not in the local modelling is pragmatic: there are reliable, average estimates available for these parameters at a regional level.

The mentioned concentrations ((PE)C_{add}) in surface water are mostly expressed as dissolved zinc concentrations. In the exposure scenarios the concentrations effluent water are expressed as total zinc concentrations. Only in the risk characterisation the total effluent concentrations are converted to dissolved effluent concentrations. The concentrations in sediment and soil are initially expressed on a wet weight (wwt) basis. Only when it is explicitly mentioned concentrations are dry weight (dwt) based.

Depending on the information submitted to the rapporteur, the (PE)C calculations start at a different level. The different levels are presented in the flowchart of Figure 3.2.2. A generic scenario is used when no specific industrial emission information is available. In that case the EU (production) tonnage is the starting point for calculating the (PE)C (entry 1). When a regional tonnage or an EU emission is available, which can be possible for the formulating and processing stages, the starting point is subsequently entry 2 or entry 3. With a regional tonnage regional emissions can be derived by multiplying it with the appropriate release fractions (A-Tables, TGD, 1996). An EU emission is divided by 10 to derive a regional emission. The justification of the use of the 10% rule in the emission estimation is explained in the paragraphs concerning the use categories of zinc chloride. Also a submitted regional emission can be an entry for the (PE)C calculation (entry 4). With this regional emission a local emission can be derived by multiplying it with the appropriate fraction of main source (B-Tables, TGD, 1996). With a local tonnage (entry 5) also local emissions can be derived by multiplying it with the appropriate release fractions (A-Tables, TGD, 1996). A site specific scenario can be used when local emissions are submitted by the industry (entry 6). The risk characterisation, i.e. the comparison of the PEC with the corresponding PNEC, should be based on the most realistic exposure information. For this, the calculated local PEC values are compared with measured local concentrations, if available (entry 7). In the next sections reference is made to Figure 3.2.2 for a better understanding of the procedures followed and entry points of the exposure assessment.

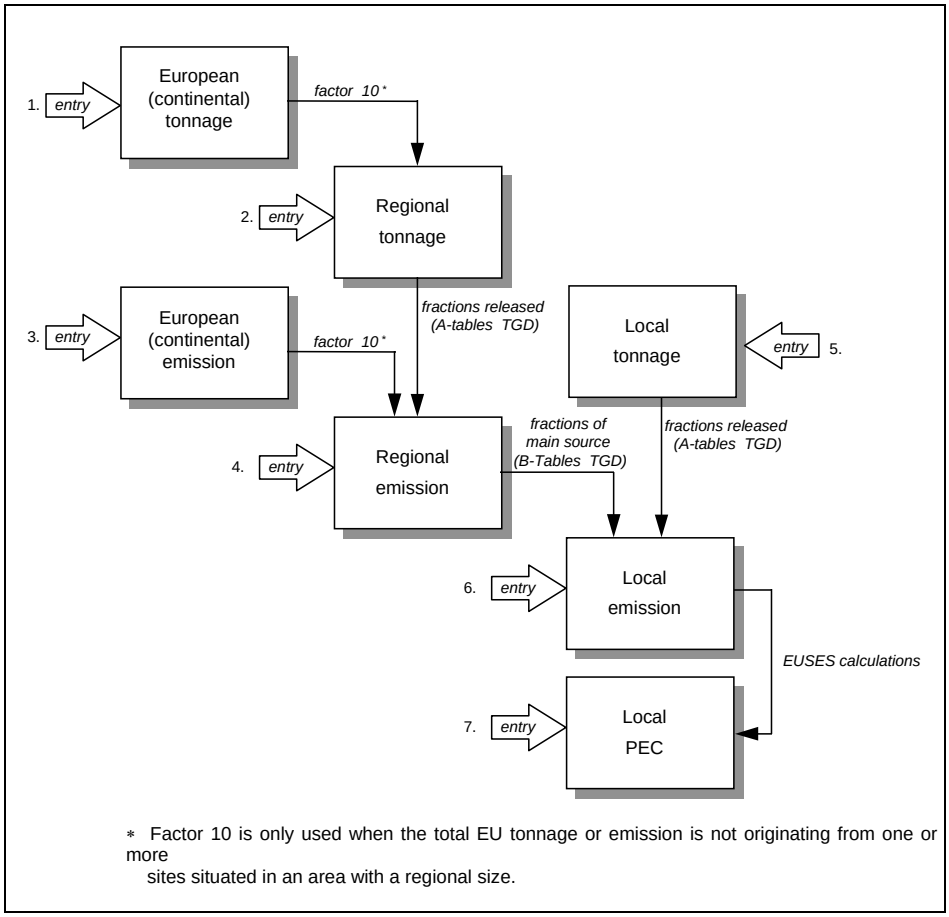

Figure 3.2.2 Flowchart for calculating the (PE)C, the entry for the calculations is depending on the submitted information.

As stated in section 2.1.1 of the RAR on zinc metal the environmental releases from waste, including mining waste, are not taken into account in the current risk assessment. The Rapporteur recognises that those releases can be significant, but the general instrumentation is currently lacking on how to deal with this type of emissions (mostly landfills).

3.2.1.2 Local exposure assessment

3.2.1.2.1 General

The local environmental exposure assessment of zinc chloride is based on the industrial releases of zinc during the following life cycle stages:

1. Production of zinc chloride
2. Processing in chemical industry
3. Processing in galvanising industry
4. Processing of zinc in the agrochemical industry
5. Processing in battery industry
6. Formulation and processing in dyes and inks

For all production plants site specific emission scenarios could be used for calculating the added concentrations (local C_{add}) in the various compartments. This because the industry submitted site specific aquatic, atmospheric and waste emission rates, as presented in Table 3.2.1.

For all formulation and processing stages, except for galvanising and the agrochemical industry, a generic scenario is used for calculating the (PE)C_{add}s (entry 1, Figure 3.2.2). Generic scenarios are only used if data are missing from either the industry or other sources in order to carry out a representative local exposure assessment.

It is emphasised that all calculated local C_{add} and PEC_{add} values are expressed as zinc, not as zinc chloride.

3.2.1.2.2 Production of zinc chloride

For all production plants site specific emission scenarios were used for calculating the local C_{add} values (entry 6, Figure 3.2.2). The emissions per annum submitted to the rapporteur are corrected for the number of production days. For the zinc chloride producers it is assumed that they produce 300 days per annum, unless otherwise mentioned. Production tonnages, aquatic, atmospheric and waste emissions submitted by the zinc chloride producing companies in the EU are presented in Table 3.2.1. Additional aquatic information submitted by the zinc chloride producing plants is presented in Table 3.2.2. This additional information is used for calculating the (PE)C_{add} values for surface water.

Table 3.2.1 Production tonnages, aquatic, atmospheric and waste emission rates for the zinc chloride producing industry in the EU for 1994/1995 (information from industry).

Company number	Production Tonnage (t/y)	Emission to air (kg Zn/y)	Emission to waste water (kg Zn/y)	Emission to water (kg Zn/y)	Emission waste (kg waste/y)
1	6,100	0	3,510 [7)]	- [10)]	1,300,000 [8)]
2	5,700	0	<350	50	<100,000
3	3,700	0	48,000	31	1,740,000 [4)]
4	12,500	<69	<8.3 [6)]	-	<3,898,000 [9)]
5	588	<1	<1350 [3) 6)]	-	1,000,000 [5)]
Total (production)	**28,600[2)]**				

1)
2) From this value about 11,600 t/y is exported out of the EU
3) Calculated with a maximum effluent concentration of 10 mg/l, an effluent discharge of 450 m^3/d and 300 working days per year.
4) Zinc content 20.5%. Waste deposited on a licensed and monitored landfill site.
5) Zinc content 15-20%. Waste deposited on a licensed landfill site, any leachate is collected and treated.
6) Waste water to municipal STP, no on site WWTP. For calculating the concentration receiving water this value is treated as the input (waste water) for the municipal STP. Emission to surface water of municipal STP is unknown.
7) 11.7 kg/d, 300 d/y, direct emission receiving water body, flow rate 3 m^3/s = 259,200 m^3/d (no onsite or post site treatment)
8) waste generated by press filtration, containing max. 20% zinc
9) zinc content in waste about 2%
10) No WWTP or STP (no onsite or post site treatment), therefore emission to waste water is emission to surface water
- unknown, no information submitted

Table 3.2.2 Additional aquatic information for zinc chloride producing plants in the EU for 1994/1995 (information from industry).

Company number	**Emission amount to water** (kg/y)	**Effluent discharge rate** (m^3/day)	**Concentration effluent (measured)** (mg/l)	**Flow rate or type of receiving water** (m^3/day)
1	3,510 [9)]	-	-	259,200
2	50	700 [8)]	0.2	63,400,000 [1)]
3	31	122	0.844	34,560 [2)]
4	<	833 [4)]	-	-
5	<	450 [4)]	10 (max) [5)]	>100,000 [7)]

1) Calculated with a submitted annual low-flow rate (10%) of 734 m^3/s
2) Calculated with a submitted annual flow rate of 0.4 m^3/s
4) On site STP effluent discharge. Effluent discharge of municipal STP is unknown
5) No on site WWTP: concentration is measured in waste water to municipal STP
7) Receiving water of the municipal STP
8) Average discharge rate, peak values are about 1000 m^3/d
9) No WWTP or STP (no onsite or post site treatment), therefore emission to waste water is emission to surface water
- unknown, no information submitted

Air

For all zinc chloride producers in the EU the site-specific emission data is used for calculating the local C_{add} values in air. Almost all companies reported that there is no emission to air.
From the daily amounts released to air the EUSES model calculates local annual average atmospheric local C_{add} values at a distance of 100 meters from a point source. The calculated local concentrations of zinc in air are presented in Table 3.2.3. The range of calculated local C_{add} values in air is $\mathbf{0 - 5.25.10^{-2}\ \mu g/m^3}$.

Water

The zinc chloride producing industry submitted aquatic emissions as waste water emissions to a local (industrial) waste water treatment plant (WWTP) or to a municipal sewage treatment plant (STP). The zinc emissions to effluent water are reduced when industrial waste water is treated in an WWTP or STP. Adsorption is the most important removal process. Other removal processes (evaporisation, degradation) are considered not to be relevant for zinc. More information about zinc in sludge is presented further on in this section. Other information about the suspended and dissolved forms of zinc is presented in section 3.2.2.1 of the zinc metal RAR.

For all production and processing stages no information is available about the adsorbed fraction of zinc in waste water belonging to a particular process. Additionally, specific information is lacking about the processes in an WWTP or STP which may have been useful to determine the adsorbed fraction of zinc. Because of this lack of information one rate of removal of zinc in an WWTP or STP will be applied to all life stages and zinc compounds. It is assumed that 74% of the total emission to waste water is directed to sewage sludge (Figure 3.2.3). This percentage is based on measured influent and effluent concentrations of communal STPs. The average removal of zinc in the examined STPs was about 74% (RIZA,

1996). In absence of specific information it is assumed that this value is also representative for the removal in industrial WWTP's. The removal rate of 74% is used for calculating the C_{add} water for the production sites for which no submitted emissions are available. The removal rate of 74% is further used for calculating the C_{add} water from the calculated waste water emissions (formulation and processing stages).

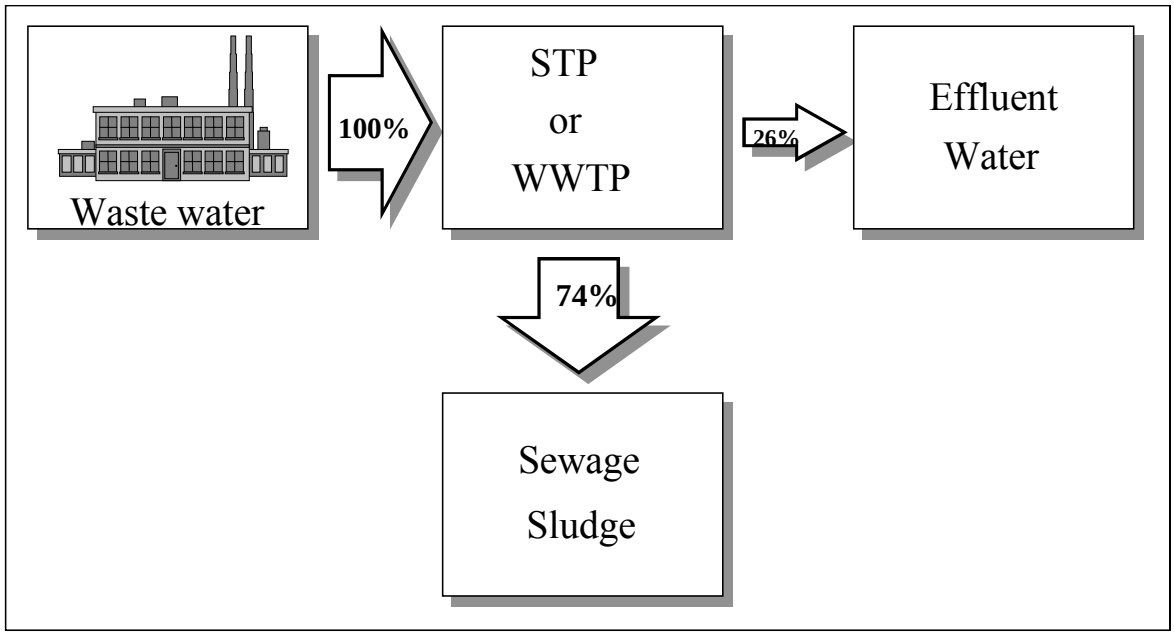

Figure 3.2.3 Distribution estimates of zinc in a WWTP or STP.

All companies submitted site specific emission data (Table 3.2.1). Additional submitted aquatic information used for calculating the local C_{add} values is presented in Table 3.2.2**.** For two companies (number 4 and 5) out of five the default size for the WWTP or STP of 2000 m^3/d is used for calculating the local C_{add} values in water. The concentration of zinc in the effluent of an STP is calculated with the equation:

$$C\,local_{influent} = \frac{EMISSION\,local}{EFFLUENT\,local_{STP}}$$

$Clocal_{influent}$:	concentration in untreated waste water (kg/m^3)
EMISSIONlocal:	local emission rate to waste water (kg/d)
$EFFLUENTlocal_{STP}$:	effluent discharge rate of local WWTP or STP (m^3/d)

$$Clocal_{effluent} = Clocal_{influent} \cdot Fstp_{water}$$

$Clocal_{effluent}$:	concentration in effluent water (kg/m^3)
$Clocal_{influent}$:	concentration in untreated waste water (kg/m^3)
$Fstp_{water}$:	fraction of emission directed to water after treatment (-)

The default dilution factor of 10 can be overwritten for site number 2 and 3, because a submitted effluent discharge rate of the WWTP and the flow rate of the river are available (see Table 3.2.2):

$$D = \frac{EFFLUENTlocal_{STP} + FLOW}{EFFLUENTlocal_{STP}}$$

D: dilution factor
$EFFLUENTlocal_{STP}$: effluent discharge rate of local WWTP/STP (m^3/d)
FLOW: flow rate of the river (m^3/d)

For company 1 and 5 the dilution factor is calculated with the submitted flow rate of the river and a default effluent flow of 2000 m^3/d. Subsequently, from the effluent concentration in the STP the local concentration of the receiving water surface water during the emission episode can be calculated with next equation. Dilution in the receiving surface water and sorption to suspended solids are taken into account.

$$C_{add}local_{water} = \frac{Clocal_{effluent}}{(1 + Kp_{susp} * C_{susp}) * D}$$

C_{add} $local_{water}$: local concentration in water during emission episode (kg/m^3)
Kp_{susp}: solids-water partition coefficient of suspended matter. For zinc 110 m^3/kg (see Partition coefficients zinc metal RAR (Stortelder et al., 1989))
C_{susp}: concentration of suspended matter in river water (0.015 kg_{dwt}/m^3, TGD)
D: dilution factor (default = 10)

For calculating the local concentrations of zinc in water emitted to estuaries or lakes a default dilution factor of 10 is assumed, unless otherwise mentioned. The calculated local concentrations of zinc in water are presented in Table 3.2.3. The range of calculated local C_{add} values in water is **$9.92.10^{-4}$ – 16.9 µg/l.**

Sediment

The local concentrations in sediment (wet weight) during emission episode can be estimated from the local C_{add} values in water, the suspended matter-water partition coefficient and the bulk density of suspended matter. The local concentrations in sediment are calculated according to the following equation:

$$C_{add}local_{sed} = \frac{K_{susp-water}}{RHO_{susp}} * PEC_{add}local_{water}$$

where: $$K_{susp-water} = Fwater_{susp} + Fsolid_{susp} * Kp_{susp} * RHOsolid$$

C_{add} $local_{sed}$: concentration in sediment during emission episode (kg/kg_{wwt})
$K_{susp\text{-}water}$: suspended matter-water partition coefficient (calculated $2.75.10^4$ m^3/m^3)
RHO_{susp}: bulk density of suspended matter (1150 kg_{wwt}/m^3)
$Fwater_{susp}$: fraction of water in suspended matter (0.9)
$Fsolid_{susp}$: fraction of solids in suspended matter (0.1)

Kp_{susp}: solids-water partition coefficient of suspended matter. For zinc 110 m^3/kg

(see Partition coefficients zinc metal RAR (Stortelder et al., 1989))

RHOsolid: density of solid phase (2500 kg/m^3)

The calculated local concentrations of zinc in sediment are presented in Table 3.2.3. The range of calculated local C_{add} values in sediment is **0.0237 – 404 mg/kg.**

Table 3.2.3 Summary of the local production tonnages, emission rates and calculated C_{add} *values.*

Company number	Production (t/y)	Emission air (kg Zn/d)	Emission waste water (kg Zn/d)	C_{add} air ($\mu g/m^3$)	Concentr. effluent STP (total) ($\mu g/l$)	C_{add} water [6] ($\mu g/l$)	C_{add} sediment (mg/kg_{wwt})
1	6,100	0	11.7	0	5,850	16.9 [1]	404
2	5,700	0	<0.167 [2]	0	238	$9.92 .10^{-4}$	0.0237
3	3,700	0	0.103 [2]	0	847	1.12	26.9
4	12,500	<0.23	<0.0277 [3]	0.0525	3.60 [5]	0.136	3.25
5	588	<0.0033	<4.5 [3]	$7.61.10^{-4}$	585 [5]	4.33	104

1) Used dilution factor is calculated with a submitted river flow and a default discharge rate (2000 m3/d)
2) Emission to surface water
3) Emission water after on site WWTP. For calculating C_{add} water this value is treated as emission waste water for municipal STP
5) Calculated effluent concentration of municipal STP
6) Values are calculated with the additional aquatic information for zinc chloride producing plants of Table 3.2.2

Soil

According to the TGD (1996) both the application of STP sludge on agricultural soil and the deposition from air are taken into account for calculating the zinc levels in the terrestrial compartment. For three zinc chloride production companies (number 2, 3 and 5) the WWTP or STP sludge is disposed off in controlled landfill sites (information from industry). For one company (number 1) the application of sludge to agricultural soils is not relevant, because there is no treatment at this site. Hence, for these companies only the emission to air, followed by a distribution and deposition model, is used for calculating soil concentrations. In this case the local emissions to air are the only input for calculating soil concentrations. For company 4 it is assumed that sludge is applied on agricultural soils. For the sludge part the daily waste water release is the input for the calculation of the C_{add}.. According to the TGD (1996) it is assumed that the total sewage sludge load is applied on agricultural soil.

The range of calculated local C_{add} values in agricultural soil is **0 - 0.489 mg/kg_{wwt}**. The concentrations of zinc in soils calculated at a local scale are presented in Table 3.2.4.

Table 3.2.4 Summary of the local emission rates and calculated C_{add} values for agricultural soils

Company number	**Emission air** (kg Zn/d)	**Emission waste water** (kg Zn/d)	**C_{add} agricultural soil** (mg/kg_{wwt})
1	0	47.3 [3]	0
2	0	<0.167 [1]	0 [2]
3	0	0.103 [1]	0 [2]
4	<0.23	<0.0277	0.489
5	<0.0033	<4.5	$2.89.10^{-4}$ [2]

1) Emission to surface water
2) WWTP/STP sludge is not applied on agricultural soils, only the emission to air has been taken into account
3) No WWTP or STP treatment and therefore no application of sludge to soil

Sludge

In a WWTP or STP the adsorbed fraction is mainly removed by precipitation. The concentration in dry sewage sludge can be calculated according to the equation:

$$C_{sludge} = \frac{Fstp_{sludge} * Elocal_{water}}{SLUDGERATE}$$

where: $$SLUDGERATE = \frac{2}{3} * SUSPCONC_{inf} * EFFLUENT_{STP} + SURPLUSsludge * Nlocal$$

C_{sludge}: concentration in dry sewage sludge (kg/kg_{dwt})
$Fstp_{sludge}$: fraction directed to sludge by STP (0.74, see Figure 3.2.3)
$Elocal_{water}$: local emission rate to waste water during episode (kg/d)
SLUDGERATE: rate of sewage sludge production (calculated: 710 kg/d)
$SUSPCONC_{inf}$: concentration of suspended matter in STP influent (0.45 kg/m^3)
$EFFLUENT_{stp}$: effluent discharge rate of local STP (default 2000 m^3/d)
SURPLUSsludge: sludge per inhabitant equivalent (0.011 kg/d.eq)
Nlocal: Number of inhabitants feeding local STP (10,000 eq)

The calculated concentrations in dry sewage sludge range from 29 to 2,730,000 mg/kg_{dwt}. The rapporteur realises that the above mentioned maximum sludge concentration exceeds the theoretical maximum, mainly as a result of a relative small STP-size and a rather high emission to water. Further it must be mentioned that the equation above is probably not appropriate for industrial WWTPs. The issue, however, is not relevant for most zinc chloride producers as their sludge is not applied on agricultural soils. Only the sludge from the site with the lowest calculated concentration of 29 mg/kg_{dwt} is assumed to be applied on agricultural soil.

Waste

Waste is formed during the production of zinc chloride. The waste, resulting from purification and cleaning of the raw material, is mainly the used flux solution and contains essentially iron compounds ($Fe(OH)_3$). Techniques are available to remove the iron compounds and to re-use the solution. All precipitations resulting from the cleaning processes are stored in controlled dump sites. Quantities of waste vary to a great extent, depending on the zinc content of the secondary raw materials (more details are not given as they are confidential).

Production company 2 operates its own waste disposal site for many years. The generated low-zinc containing sludges are deposited here. In 1995 this site was modernised and can be legally used until 31-12-2013. Any leachate is collected on-site and redirected to the same waste water treatment plant as the production waste water. According to the company no leaching is possible to groundwater and additional entries by leachate can also be excluded.
As only for one company information on their waste disposal is available, emissions from waste can not be excluded for the EU.

Emissions from waste storage sites are not taken into account for calculating the local C_{add} values (see general note on waste in section 3.2.1.1).

3.2.1.2.3 General information on the use categories of zinc chloride in the EU

Zinc chloride is mainly used in the EU in the chemical industry, galvanising industry, battery industry and as a pesticide (fungicide) in the agriculture (information from industry). The distribution and EU tonnage of these use categories in the EU are presented in Table 3.2.5.

Table 3.2.5 Distribution and EU tonnage for the different use categories of zinc chloride in the EU for 1999 (based on information from industry).

Use category	Fraction	EU tonnage
Chemical industry	± 37%	6,237
Galvanising industry	± 28%	4,721
Agrochemical industry (intermediate)	± 13%	2,205
Battery industry	± 15%	2,615
Dyes and inks industry	± 7%	1,260
Total (excl. export)	**100%**	± **17,000**

The EU production tonnages were submitted by the zinc chloride industry. When relevant (and justified) the EU production tonnages for the use categories are divided by 10 (the so-called 10% rule) to obtain regional tonnages. With the regional tonnages regional emissions are obtained, when the release fractions are applied (A-tables, TGD 1996).

With the regional emission values local values are calculated by multiplying them with the fraction of main source and with a correction factor for the number of processing days (B-tables, TGD, 1996). See Figure 3.2.2, page 14, entry 1. The regional tonnage for this life cycle stage is used as input to obtain the fraction of main source. With the local emission values local C_{add} values are calculated for each compartment as described earlier in the production section 3.2.1.2.2 (page 15).

For the soil compartment both the application of STP sludge on agricultural soil and the deposition from air are taken into account according to the TDG (1996). In the TGD (1996) it is assumed that the total sewage sludge load is applied on agricultural soil. For the sludge part the daily waste water release is the input for calculating the C_{add}. The waste water releases are calculated from the submitted effluent water releases in which it is assumed that zinc is removed in the STP for 74% (see section water of paragraph 3.2.1.2.2 and Figure 3.2.2).

3.2.1.2.4 Processing in the chemical industry

No data were submitted on the releases of zinc chloride to air and water in the chemical industry in the EU. It is not clear whether all the uses of the substance in the chemical industry (see Table 2.2.1) are equivalent. According to the latest information from industry the use of zinc chloride involves primarily the synthesis of other zinc compounds such as zinc distearate and other zinc containing products (IC3/UC33). It cannot be fully excluded that zinc chloride is also used in IC2 (basic chemicals), but this will only occur at minor quantities. The exposure assessment will be focused on the chemical intermediate scenario 3/33. For the use category IC 3 a generic scenario is carried out, starting with the EU production tonnages for the life cycle stages after production (entry 1, Figure 3.2.2). The 10% rule is used for this scenario, although no appropriate data on the number of processing sites, the size distribution of the sites and their geographic distribution are submitted to the rapporteur. However, according to expert judgement this scenario is assumed to have a wide dispersive character, justifying the use of the 10% rule. The scenario used to obtain local C_{add} values is described in section 3.2.1.2.3 (page 22). Table 3.2.6 contains the input data and results of the local exposure assessment for processing in the chemical industry.

Table 3.2.6 Input data and results for the local exposure assessment for processing of zinc chloride in the chemical industry.

	processing, generic scenario
Regional tonnage (t/y)	624
Industrial category / use category	3/33
Fraction released to air (A-tables TGD, 1996)	0
Fraction released to water (A-tables TGD, 1996)	0.02
Fraction of main source (B-tables TGD, 1996)	0.4
Number of days	62
Calculated local amount released to air (kg/d)	0
Calculated local amount released to waste water (kg/d)	80.5
Size of STP (m^3/d)	2,000
Dilution factor	2,592
Results	
Conc. effluent STP (µg/l)	10,500
C_{add} water (µg/l)	1.5
C_{add} air, 100m (µg/m^3)	0
C_{add} sediment (mg/kg_{wwt})	36.4
C_{add} agricultural soil (mg/kg_{wwt})	1,365

3.2.1.2.5 Processing in the galvanising industry

According to the industry zinc chloride is used in the general galvanising industry as a constituent of a flux coating to make the steel surface capable of wetting by liquid zinc. For the galvanising industry it is not possible to make a clear distinction between the zinc emission from either metallic zinc or from zinc chloride. Hence, for the exposure assessment of zinc chloride in the galvanising industry the reader is referred to the zinc metal RAR.

3.2.1.2.6 Processing of zinc chloride in the agrochemical industry

To the knowledge of industry zinc chloride is only used in the agrochemical industry at one site in the EU, with a volume of less than 2,100 tonnes/year. This site covers (almost) the entire EU volume (2205 t/y), therefore only one site specific scenario is carried out for the agrochemical industry. Zinc chloride is used in the agrochemical industry for the production of zinc containing pesticides, such as the fungicides Zineb and Mancozeb. Industry indicated that processing of zinc chloride (as an intermediate) in this particular category is a more appropriate term than formulation. Because of this the IC/UC combination 3/33 is selected for the generic scenario. Zinc chloride may be present in the end-product as an impurity.

The submitted site specific emission rates for this company are presented in Table 3.2.7. It must be noted that the site specific emission to waste water is very high with a volume of 49.2 tonnes zinc for 1999. With a site specific WWTP elimination rate of 72.3%, the emission to surface water (river Rhine) is 13.6 t/y. The site specific scenario is based on the submitted effluent concentration of the local WWTP. The calculated concentrations (according to entry 7, Figure 3.2.2) and calculated dilution factor are presented in Table 3.2.7. The scenario used to obtain local C values is described in section 3.2.1.2.3 (page 22).

It should be noted that for the local exposure assessment direct emissions to agricultural soil via pesticides are beyond the scope of the TGD. Diffuse emissions via this route are accounted for in the regional exposure assessment (see zinc metal document).

Table 3.2.7 Input data and results for the local exposure assessment for the processing of zinc chloride in the agrochemical industry.

	Processing site specific (1999)
Tonnage (t/y)	not applicable
Industrial category / use category	3/33
Local amount released to air (t/y)	0 [4)]
Local amount released to waste water (t/y)	49.2 (=164 kg/d)
Local amount released to receiving water (t/y)	13.6 (=45.3 kg/d)
Size of STP (m^3/d)	424,170 [1)]
Flow rate or type of receiving water (m^3/d)	63,400,000 [2)]
Dilution factor	150
Conc. effluent WWTP (µg/l)	88 [1)] (average) 48-145 [1)] (range)
Results	
C_{add} water (µg/l)	0.22 (average) 0.12-0.36 (range)
C_{add} air, 100m (µg/m^3)	0
C_{add} sediment (mg/kg_{wwt})	5.27 (average) 2.87-8.69 (range)
C_{add} agricultural soil (mg/kg_{wwt})	0 [3)]

1) Submitted by the industry (1999 data);
2) Calculated with a submitted annual low-flow rate (10%) of 734 m^3/s (Rhine);
3) No sludge application on soils. Sludge is incinerated and residues are stored on authorised landfill sites;
4) Submitted by the industry (1994 data).

3.2.1.2.7 Processing of zinc chloride in the battery industry

According to industry there are only two major sites in EU processing zinc chloride in the battery industry. For one major site information is available. A German battery producer uses annually a volume of approximately 315 tonnes of zinc chloride. According to this battery producer the annual emission of zinc to air is only "a few grams" and there is no emission to water. The emission to air is filtered and due to the sealed containment no emission to water is possible. For the PEC calculations an atmospheric emission of 1 gram per day is used.

No data were submitted on the releases of zinc chloride to air and water for the remaining processing sites in the EU. Hence, also a generic scenario is carried out, starting with the EU production tonnages for this life cycle stage (entry 1, Figure 3.2.2). Zinc chloride ends up into or onto the matrix and therefore main category 2 is used for this scenario. The 10% rule is used for this scenario, although no appropriate data on the number of processing sites, size distribution of the sites and their geographic distribution are submitted to the rapporteur. However, according to expert judgement this scenario is assumed to have a wide dispersive character, justifying the usage of the 10% rule. As the German site with a processing volume

of 315 t/y is characterised as a major site (see above), the assumption is that, apart from one other major site, there must also be a number of smaller sites. Such a smaller site is assumed to be covered in the current generic scenario where a processing volume of 262 t/y is used in combination with a default fraction of main source of 0.5.

The scenario used to obtain local PEC values is described in section 3.2.1.2.3 (page 22). Table 3.2.8 contains the input data and results of the local exposure assessment for processing of zinc chloride in the battery industry. For the determination of the release fractions zinc chloride falls under the category of <100 Pa, as is mentioned in the A-tables (TGD, 1996).

Table 3.2.8 Input data and results for the local exposure assessment for processing of zinc chloride in the battery industry.

	Site-specific scenario	Generic scenario (MC 2)
Tonnage (t/y)	315 (local)	262 (regional)
Industrial category / use category	4/12	4/12
Fraction released to air (A-tables TGD, 1996)	not applicable	0.0005
Fraction released to water (A-tables TGD, 1996)	not applicable	0.0001
Fraction of main source (B-tables TGD, 1996)	not applicable	0.5
Number of days	not applicable	52
Local amount released to air (kg/d)	0.001 (estimated)	1.25 (calculated)
Local amount released to waste water (kg/d)	0	0.25 (calculated)
Size of STP (m^3/d)	not applicable	2,000
Dilution factor	not applicable	10
Results		
Conc. Effluent STP (µg/l)	0	32.5
C_{add} water (µg/l)	0	1.23
C_{add} air, 100m (µg/m^3)	$2.28.10^{-4}$	0.285
C_{add} sediment (mg/kg_{wwt})	0	29.3
C_{add} agricultural soil (mg/kg_{wwt})	$8.66.10^{-5}$	4.35

3.2.1.2.8 Formulation and processing of zinc chloride in the dyes and inks industry

Zinc chloride is used as a part of cationic dyes. No data were submitted on the releases of zinc chloride to air and water for the formulation and processing in the dyes and inks industry in the EU. It is not clear if zinc chloride is used in the synthesis to make dyes or if it is an actual substance of dyes, which could result in releases also at the processing stage. More information on this part could help to estimate the releases more accurate. Because more information is lacking a generic scenarios are carried out, starting with the EU production tonnages for these life cycle stages (entry 1, Figure 3.2.2). It is further assumed that zinc chloride is present in dyes and is therefore used in the processing step. The rapporteur is aware of the Emission Scenario Documents on paper (IC-12) and textile (IC-13), but essential information is lacking to use these documents for the release estimation (processing). Now the A-tables in the TGD are used (IC 13). The 10% rule is used for this scenario, although no

appropriate data on the number of processing sites, size distribution of the sites and their geographic distribution are submitted to the rapporteur. However, according to expert judgement this scenario is assumed to have a wide dispersive character, justifying the 10% rule.

The scenario used to obtain local C values is described in section 3.2.1.2.3 (page 22). Table 3.2.9 contains the input data and results of the local exposure assessment for formulation and processing of zinc chloride in the dyes and inks industry. As mentioned in the A-tables (TGD, 1996), for the processing stage the assumption is made that zinc chloride is not used as a colouring agent. For zinc chloride the solubility falls under the category of >10,000 mg/l, because the solubility of zinc chloride is 4320 g/l at 25°C (see Chapter 1).

However, according to the industry about 50% of the EU market is converted to insoluble zinc compounds (sulphides) and it is expected that zinc containing pigments in dyes and other colouring agents will also have a low water solubility. Therefore, for this processing scenario (IC=13) the lowest solubility category will be used of <100 mg/l instead of the >10,000 mg/l category.

Table 3.2.9 Input data and results for the local exposure assessment for formulation and processing of zinc chloride in the dyes and inks industry.

	formulation, generic scenario	Processing, Generic scenario
Regional tonnage (t/y)	126	126
Industrial category / use category	13/55	13/55
Fraction released to air (A-tables TGD, 1996)	0.0025	0.05
Fraction released to water (A-tables TGD, 1996)	0.02	0.85
Fraction of main source (B-tables TGD, 1996)	1	0.4
Number of days	300	180[1)]
Calculated local amount released to air (kg/d)	1.05	0.14
Calculated local amount released to waste water (kg/d)	8.4	238
Size of STP (m^3/d)	2,000	2,000
Dilution factor	10	10
Results		
Conc. Effluent STP (µg/l)	1,090	30,940
C_{add} water (µg/l)	41.2	1,168
C_{add} air, 100m (µg/m^3)	0.24	3.2
C_{add} sediment (mg/kg_{wwt})	985	27,920
C_{add} agricultural soil (mg/kg_{wwt})	142	4,035

1) According to B-Tables number of processing days is 50. Value of 180 days is considered more appropriate (expert judgement).

The rapporteur is aware that the concentrations in Table 3.2.9 calculated with the generic scenario are very high. Although these levels may not reflect the actual situation in absolute terms, they point to discharge rates to the environment that definitely need further attention.

3.2.1.2.9 Measured local data in the environment

The measured effluent concentrations for some zinc chloride producing companies are ranging from 0.2 mg/l to 10 mg/l.

3.2.1.2.10 Summary of results for the local exposure assessment

Company	**Conc. effluent STP (total) (µg/l)**	**C_{add} water episode (dissolved) (µg/l)**	**C_{add} sediment episode (mg/kg_{wwt})**	**C_{add} agricultural soil (mg/kg_{wwt})**	**C_{add} air (100m) ($\mu g/m^3$)**
Production companies:					
Company 1	5,850	16.9	404	0	0
Company 2	238	$9.92 .10^{-4}$	0.0237	0	0
Company 3	847	1.12	26.9	0	0
Company 4	3.60	0.136	3.25	0.489	0.0525
Company 5	585	4.33	104	$2.89.10^{-4}$	$7.61.10^{-4}$
Use categories:					
Chemical industry: processing	10,500	1.5	36.4	1,365	0
Agrochemical industry: processing	88 (48-145)	0.22 (0.12-0.36)	5.27 (2.87-8.69)	0	0
Battery industry: processing (site specific)	0	0	0	$8.66.10^{-5}$	$2.28.10^{-4}$
Battery industry: processing (generic)	32.5	1.23	29.3	4.35	0.285
Dyes and inks industry: formulation	1,090	41.2	985	142	0.24
Dyes and inks industry: processing	30,940	1,168	27,920	4,035	3.2

3.3 EFFECTS ASSESSMENT

3.3.1 Aquatic and terrestrial compartment

The ecotoxicity of zinc chloride has been studied extensively in laboratory tests, both with aquatic organisms and terrestrial organisms. The data include many short-term toxicity studies (used to derive acute LC50 and EC50 values for zinc) and many long-term toxicity studies (used to derive chronic NOEC values for zinc). A number of the aquatic toxicity data for zinc chloride were submitted by Industry ($ZnCl_2$ IUCLID data sheet, *Goldsmidt-version of 24 March 1996*). The further data were retrieved from reviews and updates (literature searches) made by Industry and the rapporteur. For a comprehensive overview of the aquatic and terrestrial toxicity of (soluble) zinc, including zinc chloride, see the RAR Zinc metal and especially the Annexes of that report; the Annexes include detailed data on the ecotoxicity data bases for (soluble) zinc.

Once emitted into the environment, zinc chloride, which has a high water solubility, will dissociate into the zinc cation and the chloride anion. The further speciation of zinc, which includes complexation, precipitation and sorption, depends on the environmental conditions. Therefore, emitted zinc chloride as well as other emitted zinc species (e.g. zinc sulphate) will contribute to the effect of the total amount of zinc in the environment, regardless of the original source or chemical form. For this reason the risk characterisation is based on zinc (regarding zinc as the causative factor for toxicity), not on zinc chloride as such. Thus, in the local risk characterisation for zinc chloride, the $PNEC_{add}$ values for zinc (see Table 3.3.1) have been compared with the local PEC_{add} values which are also expressed as zinc, but derived from the local emissions due to the production or use of zinc chloride. In the regional risk characterisation, which is not for zinc chloride specifically but for zinc from "all" anthopogenic sources, the $PNEC_{add}$ values for zinc have been compared with PEC_{add} values for zinc, the latter values derived from the sum of the regional emissions due to industrial and non-industrial sources, diffuse sources included (see also earlier in section 3.2 for further explanation). For the regional risk characterisation the reader is referred to the Risk Assessment Report on Zinc metal (RAR Zinc metal).

In the RAR Zinc metal, $PNEC_{add}$ values have been derived for zinc, on the basis of tests with soluble zinc salts (especially zinc sulphate or zinc chloride), using the "added risk approach" (see also earlier in section 3.1 of the present report for an explanation of the added risk approach). These $PNEC_{add}$ values for zinc are listed in Table 3.3.1 and used in the risk characterisation (see section 3.4).

Table 3.3.1 $PNEC_{add}$ values for zinc (from RAR Zinc metal)

Environmental compartment	**$PNEC_{add}$**	**$PNEC_{add}$ value, as Zn**	**Remark**
Freshwater (Hardness ≥ 24 mg/L) (1)	$PNEC_{add, aquatic}$	7.8 µg/l 21 µg /l	Dissolved zinc Total zinc (2)
Freshwater (Hardness <24 mg/L) (1)	$PNEC_{add, aquatic}$ softwater	3.1 µg/l	Dissolved zinc
Freshwater sediment	$PNEC_{add, sediment}$	49 mg/kg dwt 11 mg/kg wwt	Dry weight of sediment (3) Wet weight of sediment (3)
STP effluent	$PNEC_{add, microorganisms}$	52 µg/l	Dissolved zinc
Soil	$PNEC_{add, terrestrial}$	26 mg/kg dwt 23 mg/kg wwt	Dry weight of soil (4) Wet weight of soil (4)

(1) Total hardness (mg/l), as $CaCO_3$.

(2) Total-Zn concentration: calculated from the $PNEC_{add, aquatic}$ of 7.8 µg/l for dissolved zinc, a C_{susp} of 15 mg/l (according to the TGD, 2003) and a Kp_{susp} of 110,000 l/kg.

(3) For the dry to wet weight normalisation of the $PNEC_{add, sediment}$ it is assumed that wet sediment contains 10% solids (density 2500 kg/m^3) and 90% water (density 1000 kg/m^3) by volume, i.e. 22% solids by weight. These properties are set equal to those of suspended matter, thus the $PNEC_{add, suspended\ matter}$ equals the $PNEC_{add, sediment}$ (according to the TGD, 2003).

(4) For the dry to wet weight normalisation of the $PNEC_{add, terrestrial}$ it is assumed that wet soil contains 60% solids (density 2500 kg/m^3) and 20% water (density 1000 kg/m^3) by volume, i.e. 88% solids by weight.

3.3.2 Atmosphere

No data available.

3.3.3 Secondary poisoning

Based on data on bioaccumulation of zinc in animals and on biomagnification (i.e. accumulation and transfer through the food chain), secondary poisoning is considered to be not relevant in the effect assessment of zinc, see further the RAR Zinc Metal.

3.4 RISK CHARACTERISATION

3.4.1 General

The use of the added risk approach implies that in the risk characterisation the added Predicted Environmental Concentrations (PEC_{add}'s) in the various environmental compartments are compared with the corresponding added Predicted No Effect Concentrations ($PNEC_{add}$'s). In section 3.2.1.2 local concentrations are calculated for STP, soil, water, sediment and air. Except for the PEC_{STP}, these local concentrations have to be corrected for the regional background (PEC_{add} regional), according to the TGD equation $PEClocal_{add} = Clocal_{add} + PECregional_{add}$. The regional exposure assessment, including regional monitoring data is described in the RAR on zinc metal. In case measured environmental concentrations are used in the risk characterisation, either the natural background concentration has to be subtracted from the measured environmental concentration (resulting in a "PEC_{add} / $PNEC_{add}$" ratio) or the natural background concentration has to be added to the $PNEC_{add}$ (resulting in a traditional "PEC / PNEC" ratio). Finally, a correction for bioavailability is carried out in the risk characterisation stage. For those scenarios where the uncorrected PEC values would yield a PEC/PNEC ratio above 1, a (possible) bioavailability correction is made for surface water, sediment and soil (see sections 3.3.2.1.1, 3.3.2.2.1 and 3.3.3.1.1 of Zinc Metal RAR). Final conclusions of the risk assessment are based on the corresponding 'corrected' PEC/PNEC ratios.

The reader is referred back to section 3.1 for more background information on the use of the added risk approach.

For air, the average measured concentration in the Netherlands of 0.04 µg/m^3 is chosen as regional background. (The natural background component in the value of 0.04 µg/m^3 is assumed to be negligible). Preference is given to this measured value as it is the result of a valid, representative monitoring programme. Besides, this figure is within the same order of magnitude as the calculated PEC_{add}'s at regional scale (0.006 µg/m^3 for the NL-region and 0.01 for the EU-region). For soil, following the TGD, the PEC regional in natural soil has to be added as background to the local concentration. The calculated value of 0.5 mg/kg wwt is used as regional background in the current risk assessment. For water PEC_{add}'s regional (dissolved) of 6.7 µg/l or 8.8 µg/l could be chosen as background values. These concentrations are derived from the measured average 90th percentile value of 41 µg/l [1](total) for regional waters in the Netherlands in 1997, corrected for, respectively, 3 and 12 µg/l natural background. Preference is given to these measured values as they are the result of valid, representative monitoring programmes. The figure for the Netherlands is supported by data from the large EU-survey (Denzer et al., 1998) in which a average 90-percentile value of 59.2 µg/l (total) is reported for the EU during the period 1994-1998. (Shortcomings of the Denzer et al. database are discussed in section 3.2.5.3.4 of the zinc metal RAR. Although only considered as 'indicative' in the current risk assessment, the 90P value for total zinc from Denzer et al. does give some overall EU picture that is useful for comparison purposes as

[1] Natural background value of 3 and 12 µg/l are subtracted from this value and, subsequently, the total figures are re-calculated to a dissolved zinc concentration (41-3 = 38 µg/l divided by 4.3 results in 8.8 µg/l; 41-12 = 29 µg/l divided by 4.3 results in 6.7 µg/l)

described above). For comparison: the calculated $PECregional_{add}$ values (dissolved) amounts to 4.5 µg/l (12.2 µg/l total) for the NL-region and 6.2 µg/l (16.8 µg/l total) for the EU-region. The PECs sediment are calculated from the PEC water ($PEClocal_{add}$ = $Clocal_{add}$ + $PECregional_{add}$) via the equilibrium partitioning method.

For water and sediment, in the current local risk characterisation initially only the $Clocal_{add}$ values (thus without the regional PEC_{add}) will be compared with the $PNEC_{add}$. At first the local aquatic risk characterisation thus focuses on the contribution of point sources to the potential risks, thereby neglecting the contribution of diffuse sources. If the regional PEC_{add} would have been added for sediment, all local scenarios would have resulted in $PEC_{add}/PNEC_{add}$ ratios larger than 1. This because the regional PEC_{add} already exceeds the $PNEC_{add}$ of 11 mg/kg wwt. . This holds for both calculated and measured sediment concentrations. For this reason for sediment all scenarios with a $Clocal_{add}/PNEC_{add}$ ratio between 0 and 1 a **conclusion iii*** will be drawn, indicating that due to (possibly) high added regional background concentrations a risk for sediment at local scale cannot be excluded. It has to be noted that this conclusion would not be influenced by applying the generic sediment bioavailability correction factor of 0.5.

The situation is somewhat less pronounced for the surface water compartment. With a $PNEC_{add}$ of 7.8 µg/l the regional $PEC_{add}/PNEC_{add}$ would lie between 0.8 (PEC_{add} of 6.7 µg/l) and 1.1 (PEC_{add} of 8.8 µg/l). When using an (arbitrary) average bioavailability correction factor of 0.6[2] these ratios would become, respectively 0.5 and 0.7. As a result of this, it is decided that for $Clocal_{add}/PNEC_{add}$ ratios between 0.5[3] and 1 a **conclusion iii*** will be drawn, indicating that due to (possibly) high (added) regional background concentrations a local risk for water cannot be excluded. For scenarios with a surface water $Clocal_{add}/PNEC_{add}$ ratio < 0.5 the local contribution to the (added) regional background is assumed to be negligible (**conclusion ii**).

For those scenarios in which the involved process type does intrinsically not result in water emissions a **conclusion ii)** is drawn for water and sediment.

It is important to note that the above-mentioned distinction between a (normal) conclusion iii) and a conclusion iii*) is not only made because of transparency, but also because the regional background is due to a variety of zinc compounds (and thus not only the zinc compound specifically addressed in the local risk characterisation).

In section 3.4.2 of the zinc metal RAR a general reflection is given on the uncertainties in the zinc risk assessments.

[2] See Table 3.4.67 in RAR on Zinc Metal. Average of realistic worst case and average BioF for average NL data.

[3] A $Clocal_{add}/PNEC_{add}$ of between 0.5 and 1 should theoretically also be corrected for bioavailability. This would give ratios between 0.3 and 0.6 when using the correction factor of 0.6. Such ratios could just raise the overall $PEC_{add}/PNEC_{add}$ ratio, thus including the regional background, to levels above one.

Table 3.4.10 The local (PE)C_{add} values and (PE)C_{add} / $PNEC_{add}$ ratios used in the local risk characterisation of zinc chloride. The (PE)C_{add} / $PNEC_{add}$ ratios for water, soil and sediment are based on <u>no correction</u> for bioavailability.

Company	**PEC effluent STP (dissolved)**	**Cadd water (dissolved)**	**Cadd sediment**	**PEC agricultural soil**	**PEC/PNEC STP**	**Cadd/PNEC water**	**Cadd/PNEC sediment**	**PEC/PNEC agr. soil**
	(µg/l)	**(µg/l)**	**(mg/kgwwt)**	**(mg/kgwwt)**				
Production companies:								
Company 1	1,360	16.9	404	0.5	not relevant[1)]	2.2	39	0.02
Company 2	55.3	9.92E-04	0.0237	0.5	1.1	0.0001	0.002	0.02
Company 3	197	1.12	26.9	0.5	3.8	0.14	2.6	0.02
Company 4	0.837	0.136	3.25	0.989	0.02	0.02	0.3	0.04
Company 5	136	4.33	104	0.5	2.6	0.56	10	0.02
Use categories:								
Chemical industry: processing	2,442	1.5	36.4	1365.5	47	0.19	3.5	57
Agrochemical industry: processing	20.5 (11.2-33.7)	0.22 (0.12-0.36)	5.27 (2.87-8.69)	0.5	0.39 (0.21-0.65)	0.03 (0.02-0.05)	0.51(0.28-0.84)	0.02
Battery industry: processing (site specific)	0	0	0	0.5	0	0	0	0.02
Battery industry: processing (generic)	7.56	1.23	29.3	4.85	0.15	0.16	2.8	0.20
Dyes and inks industry: formulation	253	41.2	985	143	4.9	5.3	95	5.9
Dyes and inks industry: processing	7,195	1,168	27,920	4036	138	150	2685	168

1) No WWTP or STP (no onsite or post site treatment).

3.4.2 Local risk characterisation

The local (PE)C_{add} values and the corresponding (PE)C_{add} / $PNEC_{add}$ ratios are listed in Table 3.4.10. It is emphasised that these C_{add} and PEC_{add} values and the (PE)C_{add} / $PNEC_{add}$ ratios are not corrected for bioavailability (first step in bioavailability decision trees in sections 3.3.2.1.1, 3.3.2.2.1 and 3.3.3.1.1 of RAR zinc metal). The applied bioavailability correction methods are summarised in Appendix 3.4 at the end of this Chapter. Subsequent corrections for the bioavailability of zinc in water, sediment and soil (if allowed) are discussed in the sections below.

Table 3.4.11 **Error! Reference source not found.Error! Reference source not found.**finally presents the overall results of the local risk characterisation after the various bioavailability correction steps (if relevant). Bioavailability correction is only carried out in case the uncorrected (PE)C_{add} / $PNEC_{add}$ ratio exceeds one. In addition, no bioavailability correction is done for the PEC STP.

Table 3.4.11 Summary of the uncorrected and corrected local (PE)C_{add} / $PNEC_{add}$ ratios of the local risk characterisation of zinc chloride.

	Uncorrected				**Corrected**	
Company	**PEC/PNEC STP**	**Cadd/PNEC water**	**Cadd/PNEC sediment**	**PEC/PNEC agr. soil**	**Cadd/PNEC sediment**	**PEC/PNEC agr. soil**
Production companies:						
Company 1	not relevant[1)]	**2.2**	39	0.02	**20**	
Company 2	**1.1**	0.0001	0.002	0.02		
Company 3	**3.8**	0.14	2.6	0.02	**1.3**	
Company 4	0.02	0.02	0.3	0.04		
Company 5	**2.6**	0.56	10	0.02	**5**	
Use categories:						
Chemical industry: processing	**47**	0.19	3.5	57	**1.8**	**19**
Agrochemical industry: processing	0.39 (0.21-0.65)	0.03 (0.02-0.05)	0.51(0.28-0.84)	0.02	0.25 (0.14-0.42)	
Battery industry: processing (site specific)	0	0	0	0.02		
Battery industry: processing (generic)	0.15	0.16	2.8	0.20	**1.4**	
Dyes and inks industry: formulation	**4.9**	**5.3**	95	5.9	**48**	**2.0**
Dyes and inks industry: processing	**138**	**150**	2685	168	**1343**	**56**

1) No WWTP or STP (no onsite or post site treatment).

3.4.2.1 Aquatic compartment

3.4.2.1.1 STP effluent

STP effluent
The PECs STP (total) as calculated in paragraph 3.2.1.2 for the various scenarios have been re-calculated to dissolved values. This because the $PNEC_{add}$ of 52 µg/l for microorganisms is expressed as a dissolved zinc concentration.

Production
The PEC_{STP} exceeds the $PNEC_{add}$ for microorganisms at three production sites of zinc chloride **(conclusion iii)**. The PECs are based on site-specific emission data, in some cases in combination with a site-specific effluent flow rate. The conclusions are confirmed by measured effluent concentrations.

The two remaining sites (no. 1 and 4) either stated not to have a treatment facility (direct emission to surface water) or have a negligible emission to waste water **(conclusion ii).**

Use categories
The PEC_{STP} for the processing sites of zinc chloride exceeds the $PNEC_{add}$ for microorganisms in three scenarios, i.e. 'processing in chemical industry' and 'dyes and ink industry' (both formulation and processing) **(conclusion iii).** The highest PEC/PNEC ratio is 138 for the 'processing of dyes and ink'. In contrast with the production scenarios (see above), also generic scenarios have been used for the processing of zinc chloride. This due to a lack of (sufficient) site-specific data for several use categories.

For the three remaining scenarios the PEC_{STP} is lower than the $PNEC_{add}$ for micro-organisms **(conclusion ii)**.

3.4.2.1.2 Surface water (incl. sediment)

Production
Surface water. For one production site (no. 1) the $Clocal_{add}/PNEC_{add}$ ratio is > 1. As relevant data are lacking to perform a correction for bioavailability for surface water (BLM), no additional correction can be carried out for this scenario. This implies that the original surface water risk characterisation ratio from Table 3.4.10 remains unchanged **(conclusion iii)**. For all other production sites the Clocal/PNEC ratio is < 1. For all these sites, the $Clocal_{add}/PNEC_{add}$ ratio is <0.5 **(conclusion ii)**.

Sediment. For three production sites (no. 1, 3 and 5) the $Clocal_{add}$ in sediment exceeds the $PNEC_{add}$ in sediment of 11 mg/kg wwt. As relevant data are lacking to perform a site-specific correction for bioavailability in sediment (SEM/AVS method), only the generic sediment bioavailability correction factor of 0.5 can be applied for these scenarios. This implies that the

original sediment $Clocal_{add}$ from Table 3.4.10 are multiplied with a factor 0.5. After this correction the $Clocal_{add}/PNEC_{add}$ ratio remains above 1 for the three production scenarios **(conclusion iii).** All remaining sites have a **conclusion iii*** for sediment due to the (possibly) high regional background at the local scale.

Use categories
Surface water. The $Clocal_{add}$ in water for the processing sites of zinc chloride exceeds the $PNEC_{add}$ for surface water in the two 'dyes and ink industry' scenarios. As relevant data are lacking to perform a correction for bioavailability for surface water (BLM), no additional correction can be carried out for these scenarios (**conclusion iii**). The highest $Clocal_{add}/PNEC_{add}$ ratio is 150 for the 'processing of dyes and ink'. In contrast with the production scenarios (see above), generic scenarios have been used for the use of zinc chloride in the dye and ink industry. This due to a lack of (sufficient) site-specific data. The $Clocal_{add}$/PNEC ratio is <0.5 for the other use categories **(conclusion ii)**.

Sediment. For sediment the $Clocal_{add}/PNEC_{add}$ ratio is larger than 1 for four processing scenarios. It concerns the generic scenarios 'processing chemical industry', 'battery industry: processing (generic)' and 'dyes and ink industry' (formulation and processing). As relevant data are lacking to perform a site-specific correction for bioavailability in sediment (SEM/AVS method), only the generic sediment bioavailability correction factor of 0.5 can be applied for these scenarios. After this correction (multiplication the original $Clocal_{add}$ with 0.5) the $Clocal_{add}/PNEC_{add}$ ratio remains above 1 for these scenarios (**conclusion iii**).

The $Clocal_{add}/PNEC_{add}$ ratio is <1 for the use category 'agrochemical industry', but due to possibly high regional background potential risks at a local scale cannot be excluded **(conclusion iii*)**. For the scenario 'battery industry site-specific', the involved process type does intrinsically not result in water emissions and therefore a **conclusion ii)** is drawn.

3.4.2.2 Terrestrial compartment

Production
For all production sites of zinc chloride, the PEC_{add} / $PNEC_{add}$ ratios for soil are <1 **(conclusion ii)**.

Use categories
Three use category scenarios resulted in $PEC_{add}/PNEC_{add}$ ratios >1 As relevant data are lacking to perform a site-specific correction for bioavailability in soil (soil type characteristics), only the generic soil correction factor of 3 ($R_{L\text{-}F}$: ageing aspects) can be applied for these scenarios. This implies that the original terrestrial PEC_{add}s from Table 3.4.10 are divided by a factor 3. After this correction the $PEC_{add}/PNEC_{add}$ ratio for soil remains above 1 for the three scenarios (**conclusion iii**). These scenarios refer to generic scenarios ('processing chemical industry' and 'dyes and ink industry' (formulation and processing)). For the remaining scenarios ('agrochemicals' and 'battery production') the $PEC_{add}/PNEC_{add}$ ratio for soil is <1 **(conclusion ii).**

3.4.2.3 Atmospheric compartment

A quantitative risk characterisation for exposure of organisms to airborne zinc is not possible. This because there are no useful data on the effects of airborne zinc on environmental organisms and thus no PNEC for air could be derived.
The PECs in air will be used for the risk assessment of man indirectly exposed via the environment (see Human Health part of the RAR).

3.4.2.4 Secondary poisoning

Not relevant.

3.4.3 Regional risk characterisation

See RAR on zinc metal.

APPENDIX 3.4 BIOAVAILABILITY CORRECTIONS

In the first step of the risk characterisation, the local added Predicted Environmental Concentrations ($PEClocal_{add}s$) in the various environmental compartments are compared with the corresponding added Predicted No Effect Concentrations ($PNEC_{add}s$). In case this yields a PEC_{add} / $PNEC_{add}$ ratio above 1, the risk characterisation includes (if possible) a second step in which a bioavailability correction is made, see the table below for a summary of the bioavailability correction methods applied and see RAR Zinc metal sections 3.3.2.1.1 (water), 3.3.2.2.1 (sediment) and 3.3.3.1.1 (soil) for a comprehensive explanation of the derivation and application of these bioavailability correction methods[4]. In all cases the bioavailability correction is applied to the PEC_{add}, not to the generic $PNEC_{add}$, although for the resulting corrected PEC_{add} / $PNEC_{add}$ ratio it makes no difference whether the correction is applied to the PEC_{add} or to the $PNEC_{add}$.

- For water there is only a site-specific bioavailability correction, i.e. a bioavailability correction is only applied in case there are reliable site-specific data on the abiotic water characteristics that are needed to apply the BLM models. Bioavailability factors are being derived for two scenarios of abiotic conditions. One scenario refers to an average setting and the second one to a 'realistic worst case' setting. The highest bioavailability factor ($BioF_{water}$) is subsequently used in the risk characterisation by multiplying the original $(PE)C_{add}$ with this $BioF_{water}$. If a site has a discharge to seawater, no bioavailability correction is performed, as the BLM models were developed for freshwaters.
- For sediment the bioavailability correction is either site-specific (preference) or generic.
- For soil the bioavailability correction starts with the application of the generic lab-to-field correction factor (R_{L-F}) and if the corrected PEC_{add} / $PNEC_{add}$ ratio still is >1, then a further, site-specific bioavailability correction is applied.

Final conclusions of the risk assessment are based on the corresponding 'corrected' PEC_{add} / $PNEC_{add}$ ratios.

Bioavailability corrections as applied in the EU RARs on zinc and zinc compounds

Compartment	***Added* Predicted Environmental Concentration (PEC_{add})**	
	Bioavailability correction (generic)	**Bioavailability correction (site-specific or region-specific)**
Water	None	Biotic Ligand Models (BLMs) for algae, Daphnia and fish (a)
Sediment	Factor of 2 (b)	Acid Volatile Sulphide (AVS) method (c)
Soil	Factor of 3 (d) (R_{L-F})	Regression lines for invertebrates, plants and microbial processes (e)

(a) Water – BLMs: Based on the relationship between toxicity of zinc and water characteristics, e.g. pH, dissolved organic carbon (DOC) and hardness (see RAR Zinc metal Section 3.3.2.1.1 for further explanation).

(b) The PEC_{add} (or measured concentration) for zinc in sediment is divided by a generic, AVS-related correction factor of 2 to obtain the bioavailable concentration of zinc (note that in the original description of this method in section 3.3.2.2.1 of the RAR Zinc metal it is stated that the PEC_{add} is multiplied with a factor of 0.5). The corrected PEC_{add} is subsequently used in the assessment of the PEC_{add} / $PNEC_{add}$ ratio.

(c) Sediment – AVS method: Based on the inverse relationship between toxicity of zinc and AVS content in sediment (see RAR Zinc metal Section 3.3.2.2.1 for further explanation).

[4] No bioavailability correction is done for the PEC_{STP}

This method is also described as the SEM/AVS-method, as also the toxicity of other metals, i.e. Cd, Cu, Ni, Hg and Pb, referred to as Simultaneously Extracted Metals (SEM) is reduced by AVS.

(d) The PEC_{add} (or measured concentration) for zinc in soil is divided by a generic, ageing-related lab-to-field correction factor (R_{L-F}) of 3 to obtain the bioavailable concentration of zinc. The corrected PEC_{add} is subsequently used in the assessment of the PEC_{add} / $PNEC_{add}$ ratio.

(e) Soil – Regression lines: Based on the relationship between toxicity of zinc and soil characteristics, e.g. pH and cation exchange capacity (CEC) (see RAR Zinc metal Section 3.3.3.1.1 for further explanation).

4 REFERENCES

REFERENCES EXPOSURE ASSESSMENT

The reference list applies to zinc and the five zinc compounds and is presented in the zinc metal RAR.

European Chemicals Bureau

Institute for Health and Consumer Protection

European Chemicals Bureau

Existing Substances

European Union Risk Assessment Report

CAS No: 7646-85-7

EINECS No: 231-592-0

zinc chloride

$ZnCl_2$

European Union Risk Assessment Report

zinc chloride

CAS: 7646-85-7

EC: 231-592-0

PL-2

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European Union Risk Assessment Report

ZINC CHLORIDE

Part II – Human Health

CAS No: 7646-85-7

EINECS No: 231-592-0

RISK ASSESSMENT

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ZINC CHLORIDE

Part II – Human Health

CAS No: 7646-85-7

EINECS No: 231-592-0

RISK ASSESSMENT

Final Report, 2004

This document has been prepared by the Ministry of Housing, Spatial Planning and the Environment (VROM) in consultation with the Ministry of Social Affairs and Employment (SZW) and the Ministry of Public Health, Welfare and Sport (VWS), on behalf of the European Union.

The scientific work on this report has been prepared by the Netherlands Organisation for Applied Scientific Research (TNO) and the National Institute for Public Health and the Environment (RIVM), by order of the rapporteur.

Contact point:

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3720 BA Bilthoven
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Date of Last Literature Search:	**2003**
Review of report by MS Technical Experts finalised:	**2001**
Final report:	**2004**

Foreword

We are pleased to present this Risk Assessment Report which is the result of in-depth work carried out by experts in one Member State, working in co-operation with their counterparts in the other Member States, the Commission Services, Industry and public interest groups.

The Risk Assessment was carried out in accordance with Council Regulation (EEC) 793/93[1] on the evaluation and control of the risks of "existing" substances. "Existing" substances are chemical substances in use within the European Community before September 1981 and listed in the European Inventory of Existing Commercial Chemical Substances. Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of these substances if they are produced or imported into the Community in volumes above 10 tonnes per year.

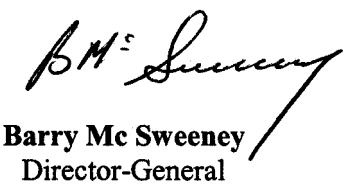
There are four overall stages in the Regulation for reducing the risks: data collection, priority setting, risk assessment and risk reduction. Data provided by Industry are used by Member States and the Commission services to determine the priority of the substances which need to be assessed. For each substance on a priority list, a Member State volunteers to act as "Rapporteur", undertaking the in-depth Risk Assessment and recommending a strategy to limit the risks of exposure to the substance, if necessary.

The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC) 1488/94[2], which is supported by a technical guidance document[3]. Normally, the "Rapporteur" and individual companies producing, importing and/or using the chemicals work closely together to develop a draft Risk Assessment Report, which is then presented at a Meeting of Member State technical experts for endorsement. The Risk Assessment Report is then peer-reviewed by the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) which gives its opinion to the European Commission on the quality of the risk assessment.

If a Risk Assessment Report concludes that measures to reduce the risks of exposure to the substances are needed, beyond any measures which may already be in place, the next step in the process is for the "Rapporteur" to develop a proposal for a strategy to limit those risks.

The Risk Assessment Report is also presented to the Organisation for Economic Co-operation and Development as a contribution to the Chapter 19, Agenda 21 goals for evaluating chemicals, agreed at the United Nations Conference on Environment and Development, held in Rio de Janeiro in 1992.

This Risk Assessment improves our knowledge about the risks to human health and the environment from exposure to chemicals. We hope you will agree that the results of this in-depth study and intensive co-operation will make a worthwhile contribution to the Community objective of reducing the overall risks from exposure to chemicals.



Barry Mc Sweeney
Director-General
DG Joint Research Centre

Catherine Day
Director-General
DG Environment

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1 O.J. No L 084, 05/04/199 p.0001 – 0075

2 O.J. No L 161, 29/06/1994 p. 0003 – 0011

3 Technical Guidance Document, Part I – V, ISBN 92-827-801 [1234]

0 OVERALL RESULTS OF THE RISK ASSESSMENT

CAS No:	7646-85-7
EINECS No:	231-592-0
IUPAC Name:	Zinc chloride

Human health (toxicity)

Workers

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Acute local effects to the respiratory tract cannot be excluded in the occupational exposure scenario “Production of zinc chloride”.

It might be possible that in some industrial premises worker protection measures are already being applied.

Consumers

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Humans exposed via the environment

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Human health (physico-chemical properties)

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

CONTENTS

TABLES

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS No: 7646-85-7
EINECS No: 231-592-0
IUPAC Name: Zinc chloride
Synonyms: Zinc dichloride, zinc(II)chloride, zinc butter, butter of zinc
Molecular formula: $ZnCl_2$
Structural formula: $ZnCl_2$
Molecular weight: 136.27

1.2 PURITY/IMPURITIES, ADDITIVES

Purity Liquid = 57.7% w/w
Solid > 96% w/w
Impurity Claimed confidential
Additives None

1.3 PHYSICO-CHEMICAL PROPERTIES

In **Table 1.1** the physico-chemical properties of zinc chloride are summarised.

Table 1.1 Physico-chemical properties of zinc chloride

Property	Result	Comment
Physical state	solid, crystalline	*
Melting point	283ºC	*
Boiling point	732ºC	*
Relative density	2.91	*
Vapour pressure	1.33 hPa at 428ºC	*
Surface tension	no data	***
Water solubility	4,320 g/l at 25ºC	*
Solubilty in other solvents	1,000 g/l ethanol; soluble in acetone; low solubilty in diethylether; unsoluble in ammonia	*
Partition coefficient n-octanol/water (log value)	no data	***
Flash point	not applicable	**
Flammability	not flammable	**
Autoflammability temperature	not-autoflammable	**

Table 1.1 continued overleaf

Table 1.1 continued Physico-chemical properties of zinc chloride

Property	Result	Comment
Explosive properties	not explosive	**
Oxidizing properties	not oxidizing	**

* More than one apparently independent source. No methods are specified.
** Conclusion based on theoretical and/or structural considerations.
*** Acceptable on theoretical and / or structural considerations.

These data are mainly derived from CRC Handbook of Chemistry and Physics (1995), Sax's Dangerous Properties of Industrial Materials (1984), Patty's Industrial Hygiene and Toxicology (1981), Römpp Chemie Lexikon (1995), and Ullmann's Encyklopädie der Technischen Chemie (1983). For an extended description see HEDSET.

Conclusion

Data on surface tension and partition coefficient were not provided. In view of the nature of the substance, determination of these parameters is considered to be irrelevant (dissociation). Information on flammability, explosive properties and oxidizing properties is not available. However, on theoretical considerations the compound is concluded to be not flammable, not explosive and not oxidizing. All other required physico-chemical data were submitted. None of these data is based on test results, substantiated with reports. However, the data are considered as sufficiently reliable to fulfil the Annex VIIA requirements.

1.4 CLASSIFICATION

At the September 2002 meeting, it was agreed to classify zinc chloride for acute oral toxicity, corrosivity and irritation to the lungs. A decision on the acute inhalation toxicity was not taken (postponed to a next meeting).

Classification and labelling according to the 29th ATP of Directive 67/548/EEC[4]:

Classification

Xn; R22
C; R34
N; R50-53

Labelling

C; N
R: 22-34-50/53
S: (1/2-)26-36/37/39-45-60-61

R22 Harmful if swallowed
R34 Causes burns

[4] The classification of the substance is established by Commission Directive 2004/73/EC of 29 April 2004 adapting to technical progress for the 29th time Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances (OJ L 152, 30.04.2004, p.1, corrigenda, OJ L 216, 16.06.2004, p.3, OJ L236, 07.07.2004, p.18).

R50/53	Very toxic to aquatic organisms. May cause long-term adverse effects in the aquatic environment.
S1/2	Keep locked up and out of the reach of children
S26	In case of contact with eyes, rinse immediately with plenty of water and seek medical advice
S36/37/39	Wear suitable protective clothing, gloves and eye/face protection
S45	In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible)
S60	This material and its container must be disposed of as hazardous waste
S61	Avoid release to the environment. Refer to special instructions/Safety data sheets

Specific concentration limits

Concentration	*Classification*
$C \geq 25\%$	C, N; R22-34-50/53
$10\% \leq C < 25\%$	C, N; R34-51/53
$5\% \leq C < 10\%$	Xn, N; R36/37/38-51/53
$2.5\% \leq C < 5\%$	N; R51/53
$0.25\% \leq C < 2.5\%$	R52/53

2 GENERAL INFORMATION ON EXPOSURE

(will be added later)

3 ENVIRONMENT

(will be added later)

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.1 General discussion

Zinc chloride melts at 283°C and boils at 732°C. It is very hygroscopic, and extremely water soluble and corrosive. It is commercially made by the reaction of aqueous hydrochloric acid with scrap zinc materials or roasted ore. The solution is purified in various ways depending upon the impurities present. The substance is mainly used in chemical synthesis, the production of pesticides, in flux baths in galvanising (zinc electroplating is often done with a chloride bath) and it is used in batteries. In medicine it is used in antiseptics, deodorants, dental cements and disinfectants. Zinc chloride solution dissolves vegetable fibres and is widely used in mercerising cotton, swelling fibres, dyeing, parchmentising paper. Other uses are in textile preservation, use in adhesives, and embalming fluids, in organic synthesis, as a dehydrant, in rubber vulcanisation and in oil refining (Kirk Othmer, 1982c).

The dustiness of zinc chloride is very low. Total dustiness was measured by the modified Heubach Dust meter to be 1.14 mg/g, with 99.66% larger than 15.8 μm (Deutsche Montan Technologie, 2000).

Occupational limit values

In several countries there are occupational limit values for zinc chloride (see **Table 4.1**).

Table 4.1 Occupational limit values for zinc chloride

Country / organisation	8-hour TWA (mg/m^3)	15-min STEL (mg/m^3)	References
USA	1	2	ACGIH (1991)
The Netherlands	1	-	SZW (1997)
UK	1	2 a)	HSE (1998)
Sweden	1 b)	-	National Board of Occupational Safety and Health, Sweden (1993)
Denmark	0.5	-	Arbejdstilsynet, 1992

a) This value is a 10 minutes-STEL
b) This TWA is determined for dust

4.1.1.2 Occupational exposure

Exposure to zinc chloride may occur during the manufacturing and the use of solutions containing zinc chloride, by the inhalation or dermal route.

The following data are used for occupational exposure assessment:

- physico-chemical data, physical appearance and vapour pressure,
- data regarding the production process and use pattern of the products and amount of the zinc compound in the product,
- exposure data from the hedset,
- measured data for zinc compounds or analogues,
- results from exposure models (EASE model).

The exposure is assessed using the available information on substance, processes and work tasks. More detailed information on these parameters may lead to a more accurate exposure assessment.

In this part of the assessment, external (potential) exposure is assessed using relevant models and other available methods in accordance with the Technical Guidance Document (TGD) and agreements made at official Meetings of Competent Authorities. Internal dose depends on external exposure and the percentage of the substance that is absorbed (either through the skin or through the respiratory system).

The exposure is assessed without taking account of the possible influence of personal protective equipment (PPE). If the assessment as based on potential exposure indicates that risks are to be expected, the use of personal protective equipment may be one of the methods to decrease actual risks, although other methods (technical and organisational) are to be preferred. This is in fact obligatory following harmonised European legislation.

Knowledge of effectiveness of PPE in practical situations is very limited. Furthermore, the effectiveness is largely dependent on site-specific aspects of management, procedures and training of workers. A reasonably effective use of proper PPE for skin exposure may reduce the external exposure with 85%. For respiratory protection the efficiency depends largely on the type of protection used. Without specific information, a tentative reduction efficiency of 90% may be assumed, equivalent to the assigned protection factors for supplied-air respirators with a half mask in negative pressure mode (NIOSH, 1987). Better protection devices will lead to higher protection. Imperfect use of the respiratory protection will lower the practical protection factor compared to the assigned factor. These estimations of reduction are not generally applicable “reasonable worst-case” estimations, but indicative values based on very limited data. They will not be used directly in the exposure and risk assessment. Furthermore, the reduction of external exposure does not necessarily reflect the reduction of absorbed dose. It has to be noted, that the use of PPE can result in a relatively increased absorption through the skin (effect of occlusion), even if the skin exposure is decreased. This effect is very substance-specific. Therefore, in risk assessment it is not possible to use default factors for reduction of exposure as a result of the use of PPE.

In some specific situations the model estimates with normal assumptions for input parameters in the assessed exposure scenarios are expected not to lead to a reasonable assessment of exposure. For situations with high risk of direct acute effects, such as manual handling of corrosive substances and hot materials, or possible inhalation exposure of substances with severe acute effects on the respiratory tract, the total level of containment given by all exposure control measures is assumed to be higher than for similar scenarios with other substances. For estimating a single day exposure an extra protection is assumed, reducing exposure with 90%. The extra protection can be reached by a combination of technical and organisational control measures and

personal protective equipment. If the extra protection is reached (mainly) by using personal protective equipment, this is an unwanted situation that should be changed by further technical and organisational control measures.

The estimate of repeated dermal exposure depends on the knowledge of a "maximum non-corrosive concentration". If such a concentration can be estimated, this concentration will be used in estimating repeated dermal exposure. Otherwise the estimate for single day exposure will be used.

Zinc chloride flux solutions are primarily made from secondary raw materials like flux solutions containing considerable amounts of zinc chloride.

The main result of the estimations is the so called reasonable worst-case estimate. This value intends to estimate the exposure level in a reasonable worst-case situation, i.e. in a situation with exposures in the higher ranges of the full distribution of exposure levels, but below the extremes reached. If a large number of suitable data is available, a 90^{th} percentile is generally used as an estimator of the reasonable worst-case value. If limited data sets are available (e.g. only measurements from one site or only small numbers of measurements or measurements with very little detail on tasks, working conditions, etc.) often the highest measured value is taken or the results of modelling are preferred or a conservative intermediate value is chosen to account for the weaknesses in the different data sets.

From the uses of zinc chloride the following scenarios for exposure will be discussed:

- Scenario 1: Production of zinc chloride,
- Scenario 2: Use of zinc chloride in galvanising.

4.1.1.2.1 Scenario 1: Chemical industry; production of zinc chloride

Zinc chloride is produced as a crystalline powder or as a ready to use solution, to be used in the galvanising industry. It is also produced (combined with NH_4Cl) as a flux crystalline powder or ready to use flux solution. Initial materials are zinc raw materials (solid and solutions) or old flux solutions which are recycled. Production is batch wise in reactors. The solutions are vacuum dried to powder. Exposure to dust can occur during packing of the powder. Zinc chloride is hygroscopic in nature and is produced in a crystalline form. Solutions are packed in intermedial bulk containers (ca. 1 m^3 capacity) or as a solid in 25 kg bags. The dustiness of $ZnCl_2$ is low compared with ZnO. ZnO has a dustiness of 30.00 mg/g whereas $ZnCl_2$ has a dustiness of 5.69 mg/g. The dustiness of $ZnCl_2/NH_4Cl$ is 19.21 mg/g. In addition, the particle size distribution of particles $ZnCl_2$ that become airborne is larger than that of ZnO (Armbruster, 2000). The dustiness of zinc chloride has also been tested by the modified Heubach method. The total dustiness was measured to be 1.14 mg/g, with 99.66% larger than 15.8 μm (Deutsche Montan Technologie, 2000).

Measured data

Data were submitted by one producer (Company A, 1999). Samples were taken as personal samples or in the vicinity of the kettles. One full shift personal sample was 0.13 mg $ZnCl_2/m^3$ and two static full shift samples were 0.013 and 0.41 mg $ZnCl_2/m^3$. Three short-term values were 0.002, 0.017 and 3.78 mg $ZnCl_2/m^3$, respectively. The EBRC has submitted data on occupational inhalation exposure during zinc chloride production (bagging and drumming operations) during full shift and short-term periods (EBRC 2001b, 2001c). Two companies submitted data. The full

shift median (n = 16) is 0.1 mg Zn/m^3 with a 90th percentile of 0.35 mg Zn/m^3. The range of the data is cited as 0.02-0.35 mg Zn/m^3. Short-term exposure reported by one company (n = 10) has a median of 0.4 mg Zn/m^3 and a 90th percentile of 3.2 mg/m^3 (range 0.01-3.8 mg Zn/m^3).

Hughson and Cherrie (2001) studied dermal exposure to zinc in a number of facilities producing zinc compounds. The measurement method was repeated wet wiping of the skin at a number of places considered representative of the skin area. The recovery of the method was found to be around 100%. The study was done in two surveys. In Survey 1, the sampling for hands was done by wet wipes from the back of the hand only. In Survey 2, the palm of the hand was sampled too. Furthermore, in Survey 2, the sample for the chest was placed further from the "V" of the neck, because this sample was intended to represent exposure underneath clothing. The measured values, expressed as µg zinc/cm^2, were recalculated into mass of zinc by multiplication with the area for which a sample was considered representative.

In Survey 1, a small galvanising plant was studied. In Survey 2, a larger galvanising plant was studied. Also, in this survey a zinc refinery (primary zinc production) was studied.

Results are summarised in **Table 4.2**.

Table 4.2 Results of the measurement of zinc exposure levels in galvanising plants (Hughson and Cherrie, 2001)

Result	N	Minimum	Maximum	GM	GSD	Remarks
Survey 1 hands and forearms	12	11.6	117.8	30.5	2.0	small galvanising plant
Survey 1 whole body	12	22.1	175.8	65.6	1.9	
Survey 2 hands and forearms	19	20	139	46	1.9	large galvanising plant
Survey 2 whole body	19	26	325	103	2.1	
Survey 2 hands and forearms	14	17	377	49	2.2	zinc refinery
Survey 2 whole body	14	37	613	82	2.1	

The worker with the highest calculated whole body exposure in Survey 1 had a higher calculated exposure on the chest (82.9 mg zinc) than on hands and forearms (76.5 mg zinc), but the worker with the highest value for hands and forearms (117.8 mg zinc) had the second highest value for whole body (164.8 mg zinc).

In Survey 2, the two highest values for whole body in galvanising were found at workers who had very high values for the chest (122 and 196 mg zinc), while the first one of these workers also had 165 mg at the face. The highest whole body level in zinc refinery was found for a sinter plant machine man that had the highest value for hands and forearms and also had a high exposure to the chest (203 mg zinc)

Model estimates

The best option in the EASE model for this kind of crystalline, hygroscopic powder is probably "low dust technique" with LEV. This leads to an estimate of 0-1 mg/m^3 (zinc chloride). If it is assumed that the dusty activities take approximately 4 hours, a full shift estimate would be 0.5 mg/m^3 (zinc chloride).

The EASE model is not considered applicable for indirect dermal exposure through contaminated surfaces (including the outside of gloves). This is by far the major route of dermal

exposure for a substance that is corrosive. Direct dermal contact is controlled by technical means and PPE.

Conclusions

Inhalation exposure

Though the number of measured data is still somewhat limited and only submitted by two producers they are preferred to data estimated by the EASE model. This model does not have the ability for a good estimate of crystalline, hygroscopic powders. Moreover, part of the production is in the form of aqueous solutions. From the measured data a typical value of 0.2 mg $ZnCl_2/m^3$ and a reasonable worst-case value of 0.7 mg $ZnCl_2/m^3$ (the 90^{th} percentile) is estimated. This value agrees with the estimate made with EASE. A short-term value of 6.4 mg $ZnCl_2/m^3$ (the 90^{th} percentile short-term value) is used for the risk evaluation.

The following uncertainties should be considered when evaluating the MOS. The number of data on which the estimates are based is very limited. The model results are for "low dust technique" and not specifically for "low dust substances" and the information on the techniques for filling of bags in these facilities is limited. The level of uncertainty is therefore considerable.

Dermal exposure

Hughson and Cherrie (2001) measured dermal exposure in a number of facilities where the process and substances used lead to excellent control of potential direct exposure due to the process temperatures (both in zinc refinery and in galvanising) and the corrosive nature of the substances used (galvanising). These measurements are also considered useful for the process of production of zinc chloride. The estimate for full shift dermal exposure will be based on the approximate 90^{th} percentile of the data of the galvanising and zinc refinery facilities in the second survey, because in that survey a better sampling method was used. This value is 100 mg zinc/day for hands and forearms and 200 mg zinc/day for the whole body. The value for whole body recalculates in 420 mg zinc chloride/day. Typical values for hands and forearms and for whole body are taken from the middle of the measured range (approximate median) and are 45 mg zinc/day, respectively 95 mg zinc/day. The whole body value recalculates in approximately 200 mg/day.

The following uncertainties should be considered in the evaluation of the MOS. The measured data are for other processes. The similarity of the exposure situation may appear to be reasonable, but there are no actual data to show this. The measurements in Survey 1 of the study of Hughson and Cherrie showed similar exposure levels as those in Survey 2, although the method of Survey 1 is expected to lead to underestimation. A possible explanation, also given by Hughson and Cherrie, is that the local exhaust ventilation in the facility in Survey 2 was much better than that in the facility in Survey 1. This suggests that the exposure estimate may be underestimated.

Exposure duration for production is estimated to be up to 8 hours, with a frequency of up to 200 days per year.

4.1.1.2.2 Scenario 2: Metal industry; use of zinc chloride in galvanising

Hot dip galvanising involves the immersion of ferrous metals (e.g. steel or iron) into a 450-470°C bath of molten zinc. The steel items to be galvanised are cleaned and prepared by

successive immersions in a degreasing and acid (pickling) bath with intermediate rinsing with water. Spent pickle liquor is removed from site by specialist contractors. In a preflux bath the objects are treated with a $ZnCl_2/NH_4Cl$ solution and after drying they are ready for the hot dip galvanising. It is also possible that there is a flux blanket covering the zinc bath, necessitating the item to be dipped to pass under it. The preflux bath is maintained by adding either a zinc chloride solution from an intermedial bulk container or by adding zinc chloride crystals from 25 kg bags. The latter is done up to once per week, according to a survey of the UK Galvanisers Association (EGGA, 1999a).

Where a flux blanket is used, the flux is generally maintained by adding one bag of zinc chloride at the end of each shift.

The hot dip galvanising bath is maintained by adding 25 kg plates or 1.0t or 1.4t blocks (jumbo's of zinc). The zinc plates and jumbo blocks do not undergo processes of sawing, machining, grinding etc. which might give rise to small particles.

Exposure to zinc compounds is possible due to the maintenance of baths (inhalation and dermal) and due to the emission of compounds from the hot bath. The removal of dross from the surface of the zinc bath is done with long handled tools to prevent contact with the very hot material. This is expected not to lead to relevant dermal exposure levels.

In general galvanizing, which is operated batch-wise, exposure occurs during the dipping process and during drossing or other maintenance operations. During the actual dipping process with concurrent high-level fume generation, exposure is reduced by using effective ventilation systems which enclose the zinc-bath and by segregating the workers from the bath by the use of a shield in order to avoid splashes from the bath. In continuous hot-dip galvanizing zinc chloride is not used as a fluxing or pre-treatment agent. In addition the process requires a high standard of automation, with a concurrent lack of the types of emission that occur during dipping/drossing operations in the batch-wise process.

In the continuous electrogalvanising process the steel is immersed in acidic solution (pickling) and zinc is transferred electrolytically from soluble zinc anodes to the steel strip surface. Zinc chloride is therefore only present as an intermediate in the electrolyte solution. Consequently there is no direct handling of zinc chloride by workers in this process.

Measured data on zinc compounds

There is a study available from The Netherlands with data on zinc chloride during the hot dip galvanising process (Remijn et al., 1982). After pickling the work piece in a 15% hydrochloric acid solution the piece was dipped in a fluxing bath, a saturated aqueous solution of $ZnCl_2.2NH_4Cl$. Personal samples were taken for workers directly involved with the galvanising process. In the dusts sampled in the workplace an attempt was made to measure the composition of the metal aerosols. Total Suspended Particles (TSP) and Respirable Suspended Particles (RSP) were measured together with HCl. The amount of $ZnCl_2$ was calculated, assuming that about 70% of the zinc aerosols were present in the form of zinc chloride. The results, expressed as GM, ranged from 0.19 to 0.86 mg/m^3 $ZnCl_2$. Five workers were monitored over 5 day shifts and 3 night shifts during the full 8-hour working period. The highest concentrations were measured for the galvanisers: 0.68 and 0.86 mg/m^3. The assumption of 70% of zinc present as $ZnCl_2$ appears to overestimate the relative availability of $ZnCl_2$ if compared with other data sets.

Dufresne et al. (1988) examined the composition of aerosols in ambient air from hot-dip galvanising plants. The aerosol portion smaller than 2 μm is composed of zinc oxide, zinc

chloride, ammonium chloride and complexes of zinc chlorides, with undetermined traces of zinc hydroxide. A set of reactions was proposed to explain the results. The composition of the aerosols was quite different from one plant to another.

Industry (EGGA, 1999b) also provided results from several sources. In **Table 4.3** an overview is presented of measured data for exposure to zinc chloride.

Eurofer (2000) submitted exposure data from 11 companies involved in hot dip galvanising and electrogalvanising. Water-soluble zinc was reported as zinc, acid soluble zinc was reported as zinc oxide. Results of personal sampling are mentioned in **Table 4.3**. The HSE (2000) reported a range of 0.09 to 7.1 mg $ZnCl_2/m^3$ and a range of 0.01-7.8 mg ZnO/m^3 during galvanising and ranges of 0.004-0.05 $ZnCl_2/m^3$ and 0.006-0.05 mg ZnO/m^3 during electroplating. EBRC (2001d) submitted a data set on inhalation short-term exposure during hot-dip galvanizing. Three companies submitted data (n = 10) which showed a median value of 0.6 mg Zn/m^3, a 90^{th} percentile of 0.87 mg Zn/m^3 and a range of 0.37-0.91 mg Zn/m^3. During maintenance of the flux bath (n = 3, three companies) the median was 0.17 mg Zn/m^3. During the actual dipping process, ammonium and zinc chloride is emitted as fumes together with zinc oxide. During drossing of the zinc bath exposure may be essentially to zinc oxide.

During continuous hot-dip galvanizing and continuous electrogalvanising, exposure is in general less than in the batch-wise processes. One of the largest European producers (approx. 30% of the total capacity) presented data. During continuous hot-dip galvanizing (EBRC, 2001e) the median value of 40 samples was 0.013 mg Zn/m^3, with a 90^{th} percentile of 0.016 mg Zn/m^3. During electrogalvanising (n = 16) the median value was 0.03 mg Zn/m^3 and the 90^{th} percentile was 0.08 mg Zn/m^3.

Table 4.3 Exposure data for zinc compounds due to galvanising

Substance	Industries and tasks	Number of Samples	Exposure levels (mg/m^3) - full shift	Reference
	hot dip galvanising (dry process)			
ZnO $ZnCl_2$	various galvaniser I galvaniser II transporter dryer crane operator	n.a. 7 7 8 8 8	0.05-0.21 0.86 (GM) 0.68 (GM) 0.21 (GM) 0.19 (GM) 0.56 (GM)	Remijn et al. (1982)
ZnO $ZnCl_2$ Zn(total)	galvanising (not specified)	> 600	0.08 (typical)* 0.26 (worst case) 0.13 (typical) 0.49 (worst case) 0.14 (typical) 0.43 (worst case)	EGGA (2000)
ZnO $ZnCl_2$	galvanising (not specified), 1 site	n.a. n.a.	< 0.01-0.65 (8-hour TWA) 0.09-0.96 (8-hour TWA)	EGGA (1999b)
ZnO $ZnCl_2$	galvanising (not specified), 8 sites	n.a. n.a.	< 0.05-4.6 (8-hour TWA)** < 0.10-0.56 (8-hour TWA)	EGGA (1999b)

Table 4.3 continued overleaf

Table 4.3 continued Exposure data for zinc compounds due to galvanising

Substance	Industries and tasks	Number of Samples	Exposure levels (mg/m^3) - full shift	Reference
ZnO + $ZnCl_2$ $ZnCl_2$	galvanising (not specified), 7 sites	n.a. n.a. n.a.	0.12-0.61 (8-hour TWA) 0.09-0.15 (15 min static) <0.01-0.19 (15 min personal)	EGGA (1999b)
$ZnCl_2$ ZnO Zn 	galvanising electroplating galvanising electroplating plating treatment and coating of metals	22 17 22 22 11 23	0.09-7.1 (avg 1.3) 0.04-0.05 (avg 0.01) 0.01-7.8 (avg 0.8) 0.006-0.05 (avg 0.02) 0.004-0.04 (avg 0.01) 0.04-0.66 (avg 0.070)	HSE (2000)
Zn ZnO Zn Zn Zn	galvanising galvanising galvanising electrogalvanising	4 n.a. 2 4	0.01-0.06 < 0.01 0.01-0.4 0.003-0.07 0.006-0.097	Eurofer (2000)

n.a. = not available

* typical exposure = median of database
worst-case exposure = 90th percentile of database
short-term exposure = twice worst-case level

** an outlier of 6.6 mg/m^3 was reported

Industry reports that most measurements were done before more modern push-pull ventilation systems were introduced.

Dermal exposure is probably mainly due to contact with contaminated surfaces. The handling of pure zinc chloride will be done using gloves to protect from the corrosive action of the substance. The measured values for galvanising (Hughson and Cherrie, 2001) are already mentioned in Scenario 1.

Model estimates

The vapour pressure of an aqueous solution of zinc chloride is negligible. Inhalation exposure to dust is calculated as 2-5 mg/m^3 assuming dry manipulation and the presence of LEV. This estimate is only of importance for the adding of $ZnCl_2$ in the form of crystals to maintain the preflux bath or flux blanket. Since $ZnCl_2$ is added in the form of crystals, the estimate probably vastly overestimates the possible dust concentrations. Another option is to use "low dust technique" and LEV, leading to an estimate of 0-1 mg/m^3 zinc chloride (0.5 mg zinc/m^3).

Dermal exposure is mainly due to transfer from contaminated surfaces. This cannot be estimated by EASE. The maintenance of the flux bath is expected to lead to a relatively minor additional exposure, mainly through an indirect route.

Conclusions

Inhalation exposure

Exposure to zinc compounds in galvanising is possible due to the work in the vicinity of the hot baths and due to maintaining the preflux bath. Inhalation exposure may be mainly to aerosols containing ZnO and $ZnCl_2$. For the estimate of exposure measured data are used though some of

the measured data have been presented with very limited detail. The data presented by Jackson (1981) are considered to be of importance and are considered representative for Europe. For a typical value for the risk characterisation, the 8-hour average value is taken from the study by Jackson (1981), which is 0.1 mg/m^3 for $ZnCl_2$ and 0.1 mg/m^3 for ZnO. These averages are in the same range compared with other measured exposure data as mentioned by EGGA (1999) and HSE (1990). As a reasonable worst-case situation the 90th percentiles based on the analysis of the original data published by Jackson et al. (1981) are taken. These are 0.5 and 0.3 mg/m^3 for $ZnCl_2$ and ZnO, respectively. A reasonable worst-case short-term value of 0.87 mg total Zn/m^3 (the 90th percentile of short-term exposures) is taken from the EBRC data set. This is a data set of up to date measurements, while the set from HSE may contain rather old (and irrelevant) data. Exposure is to a complex aggregated matrix containing ammonium chloride, zinc chloride and zinc oxide. In the Jackson study, the water soluble and water insoluble material was related respectively to the $ZnCl_2$ and ZnO portion of the sample. This may not entirely be correct, as ZnO is also slightly soluble in water, which leads to an overestimate of the soluble fraction. From this study, the molar ratio ZnO/$ZnCl_2$ can be calculated, which varies between 0.007 and 71.1. The median of the ratio is 1.25 and the 25th percentile is 0.58 and the 75th percentile is 2.16. Assuming that exposure is always to a certain mixture of $ZnCl_2$ and ZnO and not to the pure substances itself, it is assumed that the ratio will vary between the 25th and 75th percentile. In the case of the 25th percentile 63.3% of the mixture is $ZnCl_2$. Recalculation of the reasonable worst-case value of 0.87 mg total zinc/m^3 results in a concentration of 1.1 mg $ZnCl_2$/m^3 ($63.3/100 \cdot 0.87 \cdot 2.08$). In the case of the 75th percentile, 68.3% is ZnO. Recalculation results in a concentration of 0.7 mg ZnO/m^3 ($68.3/100 \cdot 0.87 \cdot 1.245$).

It is assumed that 6% of the exposure levels for the general activities concerns very fine particles (< 0.52µm), leading to reasonable worst-case full-shift exposure levels to very fine dust of 0.03 and 0.02 mg/m^3 $ZnCl_2$ and ZnO respectively and reasonable worst-case short-term exposure levels to very fine dust of 0.2 mg zinc (total Zn)/m^3.

The results of the EBRC database are used to estimate exposure during the adding of $ZnCl_2$ to maintain the preflux bath (in the batch-wise process): 0.25 mg zinc chloride/m^3 (= 0.17 mg zinc/m^3). These are all coarse particles.

The following uncertainties should be considered when evaluating the MOS. The data are largely from a large-scale representative survey in the UK. If the situation is different in other EU countries, the exposure may be under- or over estimated. The chemical speciation of the short-term values is highly uncertain. The available information suggests that the value estimated for $ZnCl_2$ could be (substantially) over estimated.

Dermal exposure

In this scenario the exposure to a corrosive substance is assessed ($ZnCl_2$). The models used to estimate the dermal exposure levels are not specifically aimed at estimating exposure levels for such a situation. The total containment, a combination of technical and organisational measures and personal protective equipment, is in such a situation usually considerably better than average. The exposure levels as measured by Hughson and Cherrie (2001) are relevant. In this case the fact that PPE is worn during direct handling has to be taken into account and the effect of PPE is accounted for in the mentioned studies. All activities occurring during the measurements were included in the study. Maintenance of the flux bath (handling of zinc chloride) was not specifically mentioned by Hughson and Cherrie. However, this infrequent activity also leads to indirect exposure through contamination and its contribution to overall exposure levels is expected to be within the variation observed. The results of the second survey

will be used as a basis for the estimation, because this survey included a measurement at the palm of the hand and is therefore considered to be of better quality. The sampling method is expected to lead to reasonably valid results for hands and forearms, head and face and neck. The larger extrapolation necessary for the chest makes the use of this method for estimating exposure levels for the full chest more questionable. The approximate 90^{th} percentiles from the measurements by Hughson and Cherrie (2001) for galvanising will be used: 100 mg zinc/day for hands and forearms and 140 mg zinc/day for whole body.

The following uncertainties should be considered in the evaluation of the MOS. The measured data in Survey 2 are expected to be of better quality than in Survey 1. However, the exposure levels are comparable. Hughson and Cherrie (2001) report that the facility in Survey 2 had a much better local exhaust ventilation system than that in Survey 1. The estimate made, based on only one facility, is therefore probably an under estimation of the reasonable worst-case for less well equipped facilities.

Table 4.4 Conclusions of the occupational exposure assessment

Scenario	Activity	Frequency (days/year)	Duration (hours/day)	Inhalation exposure as zinc chloride (zinc)				Skin exposure as zinc chloride (zinc) (mg/day) *	
				Reasonable worst case (mg/m^3)‡	Method	Typical exposure (mg/m^3) ‡	Method	Reasonable worst case	Typical
1) Production of zinc chloride	*Production of $ZnCl_2$ powders and flux solutions*								
	Full shift $ZnCl_2$	100-200	6-8	0.7 (0.35)	measured	0.2 (0.1)	measured	420 (200)	200 (95)
	Short-term $ZnCl_2$	100-200	0-1	6.4 (3.2)					
2) Use of zinc chloride in galvanising	*Maintenance of flux bath*								
	$ZnCl_2$ (large particles only)	0-50	0-0.5	0.25 (0.17)	EASE	n.e.			
	Galvanising								
	Full Shift								
	$ZnCl_2$	100-200	6-8	0.5 (0.2)	measured	0.1 (0.05)	measured	290 (140)	125 (60)
	ZnO	100-200	6-8	0.3 (0.2)	measured	0.1 (0.08)			
	Short-term								
	$ZnCl_2$	100-200	0.25	1.1 (0.5)	measured/ calculated	n.e.			
	ZnO	100-200	0.25	0.7 (0.6)	calculated$	n.e.			
	Very fine particles (< 0.52 µm)**								
	$ZnCl_2$	100-200	6-8	0.03 (0.02)	measured	n.e.			
	ZnO	100-200	6-8	0.02 (0.02)	measured	n.e.			
	Very fine particles, short-term								
	$ZnCl_2$	0-50	0.25	0.07 (0.04)	measured/ calculated	n.e.			
	ZnO	0-50	0.25	0.04 (0.03)	calculated$	n.e.			

Measured = values taken from literature; EASE = result of EASE modelling; Analogy = values based upon measured data for other substances in similar use situations; n.e. = not estimated

‡ Data without parenthesis are expressed in the compound stated in column "activity" e.g. mg $ZnCl_2/m^3$, data between parenthesis are in mg Zn/m^3. Levels are recalculated to zinc by dividing by the molar weight of zinc chloride (136.3) or zinc oxide (81.4) and multiplying with the molar weight of zinc (65.38).

$ No measured data available; values extrapolated from the $ZnCl_2$-short-term value using full shift data assuming a constant ratio between $ZnCl_2$ and ZnO.

* Data without parenthesis are expressed in zinc chloride and data between parenthesis in zinc. The original data are from measured data in zinc in galvanising (scenario 1 and 2) and zinc refinery (scenario 1 only) and are recalculated by dividing by the molar weight of zinc (65.38) and multiplying with the molar weight of zinc chloride (136.3).

** Exposure to very fine particles (< 0.52 µm) is calculated from the total exposure, assuming a maximum (w/w) of 6% of very fine particles

4.1.1.3 Consumer exposure

Zinc chloride can be found in oral rinses (Boulware et al., 1985; HSDB, 1998), as astringent in cosmetics, in herbicides and in treatment against animal pathologic bacteria in toilet bowls and urinals (HSDB, 1998).

Three countries gave some information on the consumer products containing zinc chloride, but without quantitative data or more specific uses. According to the Danish Product Register (Oct. 1996) zinc chloride is used in cleaning and soldering agents. The US reported that zinc chloride is used in pesticides, as a micronutrient, and as astringent in cosmetics and medication. Germany mentioned the use of zinc chloride in rust converters, which might be available to consumers.

Apparently zinc chloride is used in several consumer products, but no details on concentration and specific use pattern were given, which makes it difficult to predict consumer exposure. Furthermore, the total daily exposure to zinc can be higher by the use of consumer products containing other zinc compounds. Zinc compounds are also known to be used in dietary supplements, which consumers can buy over the counter.

More specified information was found for zinc compounds used in the product categories paint, cosmetics and drugstore products (VVVF, 1996; Natuur en Milieu, 1984; Annema, 1988; Rundervoort, 1992; KNMP, 1996). The default-values for paint, cosmetics and drugstore products are according to the TGD (1996) or, where no defaults are available, according to the Factsheets "verf" (paint) (Bremmer and van Veen, 2000) and "cosmetica" (cosmetics) (Bremmer et al., 2001). These factsheets are developed in order to refine the CONSEXPO program. The calculations are in accordance with the TGD (1996). For the separate use scenarios, based on the default-values found, the assumption is made that there is no uptake through inhalation when using these products and that the dermal absorption of the zinc compounds from any of the consumer products considered will be 2% for zinc solutions/suspensions and 0.2% for zinc dust/powder (see also Section 4.1.2.2.6).

Remarks

The section below is identical for all six zinc compounds evaluated under EU Regulation 793/93. Specific information is available for five of the six zinc compounds under evaluation (zinc phosphate, zinc distearate, zinc oxide, zinc chloride and zinc sulphate), as well as for some other zinc compounds not under evaluation. The latter information has also been included, because consumers (knowingly or unknowingly) at the same time can be exposed to several zinc-containing products, and irrespective of the original zinc compounds in these products, exposure will ultimately be to Zn^{2+}.

Paint

- Anti-corrosive primer containing 30% zinc phosphate. Assuming a frequency of 0.5 events/year with a dermal exposure of 2.7 g (paintbrush) or 10.8 g (spraying; roughly estimated as 4 · paintbrush) primer/event, the maximum exposure will be 1.62 g zinc phosphate/year ≈ 2.25 mg Zn^{2+}/day. With a dermal absorption of 2% the uptake is estimated to be 0.045 mg Zn^{2+} /day,
- Impregnating agent containing 40% zinc naphthenate. Assuming a frequency of 0.5 events/year with a dermal exposure of 2.7 g impregnating agent/event, the exposure will be 0.54 g zinc

naphthenate/year ≈ 0.44 mg Zn^{2+}/day (percentage of zinc in zinc naphthenate is estimated at 30%). With a dermal absorption of 2% the uptake is estimated to be 0.0088 mg Zn^{2+}/day.

Cosmetics

- Eye shadow containing 10% zinc distearate (it mainly concerns glossy, emulsion like eye shadows). By an application of 10 mg/event for 3 times/day, the exposure to eye shadow is 30 mg/day, which contains 3 mg zinc distearate ≈ 0.31 mg Zn^{2+}/day. Assuming a dermal absorption of 2% the uptake is estimated to be 0.0062 mg Zn^{2+} /day,
- Sunscreen containing 10% zinc oxide (refers to a protection factor 20-25!). By an application of 9 g sunscreen/event, 3 events/day during 18 days/year the exposure will be 1,332 mg sunscreen/day, being 107 mg Zn^{2+}/day. Assuming a dermal absorption of 2% the uptake is estimated to be 2.14 mg Zn^{2+}/ day.
- Deodorant contains 10-20% large organic zinc compounds, but apparently no ZnO. The dermal exposure is 3 g or 0.5g/event by using a spray or a roll-on, respectively. In both cases the use is once a day. Maximum dermal exposure to deodorant is 3,000 mg/day ≈ 300 mg zinc compounds/day ≈ 30 mg Zn^{2+}/day (percentage of zinc in these zinc compounds is estimated at 10%). Assuming a dermal absorption of 2% the uptake is estimated to be 0.6 mg Zn^{2+}/day,
- Dandruff shampoo containing 5% zinc compounds such as zinc pyrithione and zinc omadine (5% is estimated based on other active components in dandruff shampoos). By a usage of 12 g shampoo/event for 4 times/week, the dermal exposure to shampoo will be 6,800 mg/day with a content of 340 mg zinc compounds. Assuming that 10% of these compounds consist of zinc and that the dermal absorption is 2%, the uptake via the use of dandruff shampoo will be 0.68 mg Zn^{2+}/day.

Drugstore products

- "Baby care" ointment containing 15% zinc oxide for the irritated skin (intensive ointment) or 5% zinc oxide for protective treatment when changing diapers. The assumption was made that the usage will be 50 g of the intensive ointment/year, leading to a dermal exposure of 7.5 g ZnO/year ≈ 16.5 mg Zn^{2+}/day. Assuming a dermal absorption of 2% the uptake is estimated to be 0.33 mg Zn^{2+}/day,
- Gargle containing 6.88 mg zinc chloride/ml. Assuming a use of 10 g gargle/event (≈ 10 ml/event), 4 times/day for 4 weeks/year, the exposure during these 4 weeks will be 1,120 g gargle/year ≈ 3.1 g gargle/day, which is ≈ 10 mg Zn^{2+}/day. Assuming that almost nothing will be swallowed, there is only buccal uptake via the mucous membranes. As the contact time is very short, the uptake is assumed to be very limited. Hence, with an arbitrary absorption value of 2% the uptake is estimated to be 0.2 mg Zn^{2+}/day,
- Eye drops containing 0.25% zinc sulphate (2.5 mg/ml). The assumption was made that the usage will be 2 eye drops (0.025 ml/drop)/event, 6 times/day during 4 weeks/year, leading to an exposure of 8.4 ml eye drops/year ≈ 23 mg eye drops/day ≈ 0.058 mg zinc sulphate/day ≈ 0.023 mg Zn^{2+}/day. Assuming an absorption of 2% the uptake is estimated to be 0.00046 mg Zn^{2+}/day,
- Zinc oil containing 60% ZnO, which is merely used medically for the treatment of skin disorders. The assumption was made that the usage will be 100 g/year, leading to an

exposure of 60 g ZnO/year ≈ 0.131 g Zn^{2+}/day. Assuming a dermal absorption of 2% the uptake is estimated to be 2.62 mg Zn^{2+}/day.
Remark: it is noted that with skin disorders uptake might be higher than 2%. However, how much more is not known. Besides, it is not expected that the possible higher amount absorbed will disturb the homeostatic balance (see also Section 4.1.2.2.5).

- Dietary supplements containing zinc. Results from a recent report on the food intake of the general population in the Netherlands (Hulshof et al., 1998) indicate that approximately 10% of the population uses dietary supplements, which amongst others can contain zinc. As it is not known how much zinc-containing dietary supplements are used and in what frequency, it is difficult to estimate the exposure to zinc from dietary supplements from this report.
  A dietary survey in the UK showed that < 1-3% of the participants in different age groups took zinc supplements, providing median zinc intakes of 0.3-3.4 mg/day. However, the contribution of this supplemental zinc intake to the population average zinc intakes from food and supplements combined was negligible (EVM, 1999).

Conclusion

The compound specific exposure estimates for the different zinc compounds are taken across to the risk characterisation. However, the total daily exposure to zinc can be higher since several zinc compounds are used in consumer products. Not all of these products are used regularly or at the same time (see above). It is assumed that dandruff shampoo, deodorant, eye shadow, and possibly baby care ointment will be used on a regular basis (more than once a week), resulting in a cumulative uptake of approximately 1.6 mg Zn^{2+}/day. Therefore this value will also be taken across to the risk characterisation, as this is a more realistic calculation of the daily consumer exposure to zinc.

4.1.1.4 Humans exposed via the environment

It should be noted that in this section the zinc cation is discussed, not the salt from which it originates.

4.1.1.4.1 General exposure

The most important exposure to zinc for the general population is by the ingestion of foods. Especially meat and meat products, milk and milk products, bread and starchy foods contribute to the dietary zinc intake. The average dietary intake of zinc by adults in nine European countries was reported to be 9.1-12.3 mg/day. Only for adult males in Germany and Italy a higher daily dietary intake of 14-15 mg/day was reported (Van Dokkum, 1995). These figures are confirmed for the Netherlands in a recent report on the food intake of the general population (Hulshof et al., 1998): the average daily intake of zinc is 9.4 mg with a minimum of 0.6 mg and a maximum of 39 mg. The 95th percentile value is 15.4 mg (P_5 = 4.7, P_{10} = 5.5, median = 9.0, P_{90} = 13.8). The intake figures are based on a random group of 6,250 persons.

The differences in zinc intake vary due to source and variety of the food.

An epidemiological study has been carried out by Kreis (1992) in which the health effects of cadmium (and zinc) were investigated in a contaminated area in the southern part of the Netherlands (Kempenland). A population sample aged 30-69, with a residence of at least

15 years in a rural village in Kempenland (NL) was compared with a control population of an unpolluted area. About 75% of the inhabitants of both areas consumed at least half of their vegetables from local gardens. The plasma concentration of zinc did not different between the exposed (n = 299) and the reference population (n = 295) after adjustment for age and gender. The author concluded that, in contrast to cadmium, zinc exposure probably did not differ between the two villages.

In the section on measured regional data in the environment in the zinc metal risk assessment report, national monitoring data are presented for groundwater, surface water and air. In the following a compilation of these data is given. Via the National Soil Monitoring Network maximum zinc concentrations in upper groundwater of 1.1 mg/l (cattle farms) and 3.1 mg/l (forest locations) have been reported in the Netherlands. Recent zinc concentrations in large surface water in the Netherlands are found to be all below 0.1 mg/l. Recent atmospheric zinc concentrations in the Netherlands are below 0.1 μg/m^3 (annual averages). Higher concentrations, up to 14 μg/m^3, were reported for Belgium (older data).

Under normal conditions, drinking water and ambient air are minor sources of zinc intake. Cleven et al. (1993) estimated the intake by drinking water and ambient air to be < 0.01 mg/day and 0.0007 mg/day, respectively. The monitoring data above indicate somewhat higher intakes, but it is to be noted that nowadays in the EU upper groundwater and large surface water are not directly representative for drinking water. In the Netherlands, monitoring of zinc in drinking water is ceased (at water companies) or about to be ceased (at pump stations) (personal communication by RIVM-LWD, 1999).

Conclusion

The recent average dietary intake of zinc is around 10 mg/day. This value is taken across to the risk characterisation. Compared to this intake via food, intake via drinking water and ambient air is considered negligible.

4.1.1.4.2 Local exposure

Estimated local zinc concentrations in water and air around industrial facilities

In surface water maximum local zinc concentrations (PEC_{add}s) of 45.6 μg/l and 3,154 μg/l (total zinc) have been estimated for the production and processing of zinc chloride, respectively (see Section on local exposure assessment in the environmental part).

Maximum atmospheric zinc concentrations (PEC_{add}s) are 0.0525 μg/m^3 and 3.2 μg/m^3, for production and processing, respectively (see Section on local exposure assessment in the environmental part).

Conclusion

The PEC_{add}s mentioned above are taken across to the risk characterisation.

4.1.2 Effects assessment: Hazard identification and Dose (concentration) - response (effect) assessment

4.1.2.1 Introduction

Basic assumptions

Large parts of the hazard section are identical in the risk assessment reports on the six zinc compounds now under review under EU Regulation 793/93. This is because of the basic assumption that the zinc cation (as measure for dissolved zinc species) is the determining factor for systemic toxicity.

It is realised that for zinc (and other metal) compounds it would be important to define the actual or bioavailable concentration which is important for toxicity, both in laboratory animals and in humans. Due to several physico-chemical processes, zinc will exist in different chemical forms, some of which are more bioavailable than others. It is thus realised that the bioavailability is affected by various physico-chemical parameters (ionic behaviour, solubility, pH, alkalinity etc.). Although there is some information on the solubility of the six zinc compounds (they are soluble in water (sulphate, chloride) or in diluted acids (phosphate, distearate and oxide) and elemental zinc is attacked by HCl to yield Zn^{2+} (Windholz et al., 1983)), adequate information is lacking how to quantitatively determine or estimate the bioavailable fraction of all the different zinc compounds in either laboratory animals or humans. Therefore, it is assumed that all zinc compounds (including metallic zinc) are changed (at least in part) to the ionic species (cf. TGD for environmental risk assessment for metals and metal compounds), and all toxicity data (independent of the tested compound) were used and expressed as the zinc cation.

With respect to local effects, it is not always possible to use data from all zinc compounds. Hence, for local effects only data from the specific zinc compound were used, or, where there were derogations, data from zinc compounds with more or less the same solubility characteristics.

A problem might arise for the route-to-route extrapolation for inhalation and dermal exposure, since the differences in physico-chemical properties of the zinc compounds can change the toxicokinetics (absorption) and subsequently the toxic effects. Although it is possible to predict the systemic effects after inhalation or dermal exposure from oral toxicity data of the zinc compound itself or other zinc compounds, this is only justifiable after careful consideration of all available data to establish adequate extrapolation factors.

Furthermore it is assumed that the influence of the background intake levels of zinc cations in animal studies will be the same for humans.

Database

A lot of information was provided by industry. Much additional data on zinc and zinc compounds have been published, some of which are referred to in good quality reviews by ATSDR (1994) and Walsh et al. (1994). By using these reviews plus (where relevant) the primary literature, it is felt that in the risk assessment reports most of the essential data to establish possible hazards/risk of zinc for human health have been covered. As not for all studies mentioned in the risk assessment reports the primary literature has been checked, some studies have been described in less detail than others. In the text of the risk assessment reports,

information cited from reviews is marked by a *(r)* after the reference. This information is not included in the hedset.

4.1.2.2 Toxicokinetics, metabolism and distribution

Several data were provided on the toxicokinetics of zinc chloride. Data on other zinc compounds have also been used, as the basic assumption is made that after intake all zinc compounds (including metallic zinc) are changed (at least in part) to the ionic species and that it is this zinc cation that is the determining factor for the biological activities of the zinc compounds (see Section 4.1.2.1).

4.1.2.2.1 Absorption

Oral

Studies in animals

Furchner and Richmond (1962) added zinc acetate to the diet of Sprague Dawley rats (9/group) to reach concentrations of Zn of 58 (no zinc acetate added; normal concentration in "control" feed), 117, 175, 293, 410 or 664 mg/kg via the feed, corresponding to ca. 3, 6, 9, 14.5, 20.5 or 33 mg Zn/kg bw. After 28 days the unfasted animals were dosed with 1.2 μCi of $^{65}ZnCl_2$ (ca. 0.15 ng). Whole-body radioactivity was determined at various time points up to 11 days post dosing using a whole-body gamma counter.

In the group which received the non-supplemented diet (i.e. 58 mg Zn/kg feed) ca. 20% of the administered radioactivity was retained at 24-hour post dosing which gradually decreased to about 9% at day 11. The amount of radioactivity retained at 24-hour post-dosing declined with increasing dietary zinc levels to about 13% for the group with the highest dietary zinc. In this group after 11 days only ca. 2.3% of the administered radioactivity was left. The data indicated that low dietary zinc results in increased zinc retention and that at higher dietary zinc levels absorption of zinc is reduced.

After a pre-exposure period of 7 days, male Wistar rats, kept on a semi-synthetic diet, were dosed orally with 86-130 μg ^{65}Zn as $ZnCl_2$ (n = 15), $ZnCO_3$ (n = 15) or $Zn_5(OH)_8Cl_2 \cdot H_2O$ (n = 20) added to a test meal. It was assumed that during the first 5 days post dosing non-absorbed zinc was excreted via the faeces. Absorption of labelled Zn^{2+} was calculated from *in vivo* whole-body gamma counting results over the period 5-14 days post-dosing. The uptake was calculated to be 40, 45 or 48 % for $Zn_5(OH)_8Cl_2 \cdot H_2O$, $ZnCl_2$ and $ZnCO_3$, respectively (Galvez-Morros et al., 1992).

Studies in humans

A wide range in absorption (8-80%) is observed in humans, probably due to the amount and type of food eaten (Hunt et al., 1991*(r)*; Reinhold et al., 1991*(r)*; Sandstrom and Sandberg, 1992*(r)*). Persons with adequate nutritional levels of Zn^{2+} absorb approximately 20-30% of all ingested Zn^{2+}. Those who are zinc-deficient absorb greater proportions of administered Zn^{2+} (Johnson et al., 1988*(r)*; Spencer et al., 1985*(r)*), while in persons with excessive zinc intake gastrointestinal uptake can be less (Babcock et al., 1982).

Zn^{2+} absorption in the gastrointestinal tract occurs throughout the entire small intestine with the highest rate in the jejunum and the rate of total absorption appears to be concentration dependent (Lee et al., 1989*(r)*).

The Zn^{2+} absorption process in the intestines includes both passive diffusion and a carrier-mediated process (Tacnet et al., 1990*(r)*). At low zinc concentrations a cysteine-rich intestinal protein (CRIP) is involved in this process. This protein binds Zn^{2+} entering the intestinal cells from the lumen but this process appears to be saturable. Metallothionein, a metal-binding protein (also rich in cysteine), may be involved at higher zinc concentrations (Gunshin et al., 1991*(r)*; Hempe and Cousins, 1992*(r)*; Sturniolo et al., 1991*(r)*). Zinc cations can induce metallothionein production in intestinal mucosa cells (Richards and Cousins, 1975*(r)*).

Payton et al. (1982) determined the intestinal absorption following single oral administration of ^{65}[Zn]-chloride to 6 groups of 5 healthy adult volunteers by comparison of whole body radioactivity counting and faecal excretion data. The individuals fasted overnight prior to dosing. Approximately 55% of the administered ^{65}[Zn]-chloride was absorbed at doses of 18, 45 and 90 μmol (~ 1.2, 2.9 or 5.8 mg) of zinc. The absorption was reduced with increasing dose, indicating that zinc absorption is saturable. At test dose levels of 180, 450 and 900 μmol (~ 11.6, 29 or 58 mg of Zn), only 51, 40 and 25% of the ^{65}Zn was absorbed, respectively. Additional studies in 15 in human volunteers with various intestinal diseases indicated that absorption of Zn occurred mainly in the proximal parts of the intestine.

From this study it appears that in healthy persons with intake levels differing by a factor of 10, uptake levels vary maximally by a factor of two.

The absorption of orally administered ^{65}Zn was studied in 50 patients with taste and smell dysfunction. The study was conducted in three phases. Prior to the start of the study 10 patients were admitted to a metabolic ward and put on a fixed daily diet containing 8-13 mg Zn. In the first phase all patients were studied for 21 days after receiving a single oral dose of 3-18 μCi of ^{65}Zn (~ 0.4 to 1.2 ng zinc) as $ZnCl_2$ after an overnight fast. In the second phase, which started after 21 days and continued for 290 to 440 (mean 336) days, all 50 patients received placebo. To study the effect of additional zinc intake on elimination of previously sequestered radioactivity, in the third phase of the study 14 patients continued on placebo while 36 received $ZnSO_4$ (100 mg Zn^{2+}/day) for 112 to 440 (mean 307) days. Phases two and three were a controlled clinical trial of the effects of zinc on retention of the ^{65}Zn tracer. The results of Phase two and three are described in Section 4.1.2.2.4.

Total body retention and activity in plasma and red cells were measured for all patients throughout the study. It was estimated that for the ten in-patients ca. 55% of the administered radioactivity was absorbed while for the whole group of 50 patients the absorption was approximately 60 percent (Aamodt et al., 1982).

Remark: from the study description it is not clear whether the radioactivity was administered as pure radioactive zinc chloride or whether it was diluted with unlabelled zinc chloride. As the authors stated that "patients were given 3 to 18 μCi carrier free ^{65}Zn" for the calculation of the dose of ^{65}Zn in terms of nanogram zinc, it has been assumed that all zinc administered was in fact ^{65}Zn.

The absorption of zinc from soluble zinc acetate, zinc sulphate, zinc aminoate, zinc methionine and insoluble zinc oxide was compared in ten human volunteers who were dosed orally with 50 mg Zn in various forms separated by two weeks intervals. Bioavailability of zinc from the various forms was compared on the basis of plasma zinc levels and area under the plasma curve

analysis. Plasma peak levels were observed after about 2.5 hours for all forms, but maximal plasma Zn concentration amounted to 221 and 225 µg/dl for the acetate and the sulphate form while the peak plasma level for Zn from the oxide was only 159 µg/dl. When AUC values for the different zinc forms were compared, it appeared that the bioavailability of zinc oxide was about 60% of the bioavailability of the soluble forms. Information on absolute bioavailability was not obtained (Prasad et al., 1993).

Nève et al. (1991) reported an absorption half-life of 0.4 hours when 45 mg Zn^{2+} as zinc sulphate was administered once in gelatine capsules to 10 healthy young men. Serum concentrations were measured frequently during a total investigation time of 8 hours. A mean maximum concentration of 8.2 µmol Zn^{2+}/l serum was found after 2.3 hours (t_{max}). There is evidence of an enteral recirculation, the first rebound effect appeared after 1.4 hours during the absorption phase before t_{max} was reached, and exhibited mean reabsorption rates of 70% of the dose given. The subsequent ones (max. of 5) appeared at regular intervals of 1.2 hours with a decrease of the quantity reabsorbed.

Factors that influence the gastrointestinal absorption of zinc cations include ligands (for example a decreased Zn^{2+} absorption may occur by intake of plant proteins, such as soy and phytate (Sandstrom and Sandberg, 1992*(r)*), by intake of alcohol (Antonson and Vanderhoff, 1983*(r)*) or use of EDTA (Solomons et al. 1979*(r)*; Spencer et al., 1966*(r)*)), or other trace elements in the diet (Solomons, 1988(*r*)). Also the zinc status of the body, the endogenous zinc secretion into the intestinal lumen via epithelial cells, bile and pancreatic secretion, and the intracellular transport have an influence on the Zn^{2+} absorption in the gastrointestinal tract (Cunnane, 1988*(r)*; Flanagan et al., 1983*(r)*). The mechanism by which zinc is transferred to or across the mucosal surface of the microvilli is not known (Cousins, 1989*(r)*).

Inhalation

Studies in animals

Rates or percentages of absorption of zinc cations after inhalation are not available, but there are some studies on Zn^{2+} retention in the lung.

Pistorius et al. (1976) exposed male and female rats to 15 mg ZnO dust/m^3 (particle size < 1 µm) for 4 hours/day, 5 days/week during 1 day or for 2, 4 or 8 weeks. Animals were killed 24 hours after the last exposure and the zinc content of the lungs, liver, kidneys, tibia and femur was measured. After 1 day of exposure the total zinc content of the lung in males and females was about 46 and 49 µg, respectively. In lung, liver, kidney and bone only minimal differences in tissue zinc content were seen during the experiment. As tissue zinc levels in non-treated animals were not studied, it is not clear whether tissue zinc comes from the experimental or from dietary exposure. However, as the pulmonary zinc level did not rise throughout the study it can be assumed that pulmonary deposition is very low and/or that pulmonary clearance is very high.

After exposure to 4.3 mg (rat), 6.0 mg (rabbit), 11.3 mg (guinea pig) mg ZnO (aerosol)/m^3 for 2-3 hours, the pulmonary retention in rats, rabbits and guinea pigs was 11.5%, 4.7% and 19.8%, respectively. The aerosol had a very small mass median diameter of 0.17 µm (Gordon et al., 1992).

In a time course experiment male Wistar rats (3/group) received a single intratracheal instillation of 0.4 ml ZnO suspension (ZnO particles < 2 µm, but they appeared to form aggregates of 10-20 particles) at a dose of 100 µg Zn^{2+}/rat and the rats were killed 1/3, 1, 2, 3, 5, 7, 14 and 21 days after administration. In a dose-response experiment 0.4 ml ZnO suspension (ZnO

particles < 2 μm, but they appeared to form aggregates of 10-20 particles) was instilled in the lungs of male Wistar rats (3/group) at doses of 20, 50, 100, 200, 500 and 1,000 μg Zn^{2+}/rat. The rats were killed after 2 days. Control animals were included in the experiments.

In the time course experiment a significantly increased lung wet weight 1 day after instillation and remaining throughout the time course was seen. Only a limited portion of Zn could be retrieved in the bronchoalveolar lavage fluid (BALF). No measurable amount of exogenous Zn was observed after 5 days. The half-life of ZnO instilled in the lung was calculated to be 14 hours.

In the dose-response experiment the lung wet weight increased with dose of ZnO 2 days after instillation. The results indicated that the rat lung was able to clear ZnO particles up to a dose of 50 μg Zn^{2+}/rat at least within two days. No measurable accumulation of Zn was observed in the liver and kidneys even at a dose of 1,000 μg Zn^{2+}/rat (Hirano et al., 1989).

In a study of Oberdörster et al. (1980) the lung clearance rate of zinc aerosols was determined in male Wistar rats (8/group) 0, 2, 4, 8 and 24 hours after exposure to ZnO aerosol at a concentration of 12.8 mg/m^3 (mean aerodynamic diameter of 1 μm) for 17 hours. The ZnO aerosol was created by pyrolysis of a micronised Zn-acetate aerosol at 500°C. 8 Animals were kept in clean air and served as controls. The lungs and trachea of the animals were removed and their zinc content was determined by flame photometry. In comparison with the controls, the lungs of exposed rats were increased in weight (presumably because of oedema), which increase was significant at 8 hours and even more pronounced at 24 hours. The zinc content in the trachea was not uniform but was above control values except after 24 hours. The zinc content in the lungs decreased monoexponential and was 7% of the initial burden after 24 hours. According to the short half-life of 6.3 hours found in this study for the pulmonary zinc content, a fast dissolution of the particles must occur, as the alveolar clearance of an inert Fe_2O_3 aerosol occurred with a half-life of about 34 hours. It is not clear whether the clearance of Zn from the lungs is affected by the pathological condition of the lungs.

Studies in humans

Elevated zinc concentrations in blood and urine (Hamdi et al., 1969; Trevisan et al., 1982(r)) of persons occupationally exposed to zinc oxide fumes suggest that there is some pulmonary absorption, but no quantitative human data are available.

Other

Data were provided on the particle size distribution of zinc aerosol in three different industry sectors, i.e. the galvanising sector (three plants, 4 samples each), the brass casting sector (two plants, 3 and 4 samples respectively) and the zinc oxide production sector (one plant, 10 samples), by using personal cascade impactors with cut-off diameters of 0.52, 0.93, 1.55, 3.5, 6.0 and 21.3 μm, and a final filter diameter of 0.3 μm (Groat et al., 1999). These data served as input for the Multiple Path Particle Deposition Model (MPPDep version V1.11; Freijer et al., 1999) in order to estimate the airway deposition (in head, tracheobronchial and pulmonary region) for workers, by using:

- the human – five lobar lung model,
- a polydisperse particle distribution (i.e. this distribution contains a wide range of particle sizes), by taking the mean size distribution of the 10 samples for zinc oxide production (MMAD 15.2 μm, GSD 4.0). Using this MMAD and GSD for the total polydisperse

distribution is preferred above treating the polydisperse particles on individual impactor stages (with given cut-off diameters) as being monodisperse particles, also because the maximum particle size in the MPPDep model (20 μm) is lower than the largest size fraction of the cascade impactor (21.3 μm),

- both the oral breathing and the oronasal (normal augmenter) mode, but not the nasal breathing mode. The latter is considered to present an underestimate because 1) many people are oronasal or oral breathers, independent of their activities, 2) people with a cold will not normally breath nasally, and 3) with heavy exercise, short-term deep oral breathing will occur, resulting in increased deep pulmonary deposition,
- the possibility of inhalability adjustment for the oronasal augmenter. Inhalability is defined as that fraction of particles in an aerosol that can enter the nose or mouth upon inhalation. It must be noted that inhalability is different from respirability, which term relates to the deposition of particles after making their entrance inside the airways. If "inhalability adjustment" is "off", the calculations start by assuming that the airflow is in line with the direction of the nasal entrance. However, in reality this will not be the case because the airflow has to make turns to enter the nose. This results in losses that are larger with increasing particle size. Ménache et al. (1995) have described the relations between exposure concentration and concentration at the entrance of the airways for laboratory animals and humans,
- a tidal volume and breathing frequency corresponding to the default breathing rate of 10 m^3 for an 8-hour shift (1,100 ml and 20 breaths/min, respectively). This breathing rate is more representative for light exercise activities than for more moderate or heavy exercise activities (EPA, 1997), which can be expected to take place in the zinc industry (see Section 4.1.1.2). Therefore, also a non-default tidal volume and breathing frequency corresponding to a breathing rate of 19 m^3 for an 8-hour shift have been taken (1,700 ml and 23 breaths/min, respectively, based on a breathing volume of 40 l/min for moderate exercise activities (EPA, 1997)). It must be noted that at a minute volume < 35.3 l/min for normal augmenters breathing is only through the nose, while at a minute volume ≥ 35.3 ml/min there is combined nose and mouth breathing. For oral breathers, breathing is always only through the mouth, independent of the minute volume used.

Results of the MPPDep modelling are given in **Table 4.5**. It must be noted that the MPPDep only models deposition, not clearance and retention.

Table 4.5 Deposition fractions for oral breathers and for oronasal augmenters, using a polydisperse particle distribution (MMAD 15.2 μm, GSD 4.0).

	Inhalability	Tidal volume (ml)	Breaths/ min	Deposition region			
				Head	Tracheo-bronchial	Pulmonary	Total
Oral	off	1,100 1,700	20 23	0.638 0.676	0.071 0.100	0.139 0.101	0.848 0.877
Oronasal	off	1,100 1,700	20 23	0.927 0.804	0.011 0.064	0.021 0.064	0.960 0.932
Oronasal	on	1,100 1,700	20 23	0.519 0.585	0.011 0.063	0.021 0.064	0.551 0.713

From **Table 4.5** it can be seen that for oral as well as for oronasal breathers the largest part of the deposition takes place in the head region, irrespective of the breathing rate. When inhalability adjustment is "on" head region deposition is somewhat reduced. However, the following is to be noted. As stated above, the corrections for inhalability of particles is based on relationships derived by Ménache et al. (1995). For humans this is based on experiments with only 4 healthy adult volunteers. The experiments are thus too limited to conclude for sure that this correction is valid for all human subjects and all situations (children, elderly, exercise activity, etc). It is therefore fair to estimate the deposition without inhalability adjustment to get an idea of a worst-case situation. The situation with inhalability adjustment "on" will not be taken further into account.

The fate and uptake of deposited particles depends on the clearance mechanisms present in the different parts of the airway. In the head region, most material will be cleared rapidly, either by expulsion (not the case for oral breathers) or by translocation to the gastrointestinal tract (half-time 10 min). A small fraction will be subject to more prolonged retention, which can result in direct local absorption. More or less the same is true for the tracheobronchial region, where the largest part of the deposited material will be cleared to the pharynx (mainly by mucociliary clearance (half-time 100 min)) followed by clearance to the gastrointestinal tract, and only a small fraction will be retained (ICRP, 1994). Higher uptake rates may be assumed for the pulmonary region than for the head and tracheobronchial region.

Once translocated to the gastrointestinal tract, uptake will be in accordance with oral uptake kinetics. Hence, for that part of the material deposited in head and tracheobronchial region that is cleared to the gastrointestinal tract, the oral absorption figures (20% for soluble zinc compounds and 12% for less soluble/insoluble zinc compounds, see Section 4.1.2.2.6) can be taken. However, there are no data available on zinc to estimate the part that is cleared to the gastrointestinal tract and the part that is absorbed locally in the different airway regions. With respect to the latter though, there are some data available for radionuclides. After instillation of small volumes (2-3 μl for rats, 10 μl for hamsters, 0.3 ml for dogs) of solutions or suspensions of radionuclides into each region of the respiratory tract, retention and absorption into blood was measured. For the more soluble chemical forms (a.o. citrate and nitrate) absorption values of 4.8-17.6% in the nasopharynx, 12.5-48% in the tracheobronchial region and up to 100% in the pulmonary region were found. For the more insoluble chemical forms (i.e. oxide) retention and absorption in the nasopharynx and tracheobronchial region was negligible (ICRP, 1994). There are no data on how the solubility of the different chemical forms of the radionuclides compares to the solubility of the soluble zinc compounds. Although the applicability of the radionuclide figures to the zinc compounds is not quite clear, it is probably a reasonable worst case to take the upper values found (i.e. 20, 50 and 100% in head, trachebronchial and pulmonary region, respectively) for local absorption of soluble zinc compounds. For the less soluble/insoluble zinc compounds it is probably safe to assume negligible absorption for the head and tracheobronchial region and 100% absorption for the pulmonary region. This is supported by the findings in the study by Oberdörster et al. (1980), where the dissolution halftime of 1 μm diameter zinc oxide particles in the deep lung was approximately 6 hours. Given that the clearance to the gastrointestinal tract occurs within a time frame of minutes (10-100 min in head and tracheobronchial region), there will be no significant dissolution in these areas. Besides, most of the particles in these areas will have a diameter >1 μm, thus dissolution halftimes for these larger particles will be longer.

Based on the above information, inhalation absorption was estimated by assuming the following:

	soluble zinc compounds (chloride and sulphate)	less soluble/insoluble zinc compounds (metal, oxide, phosphate, distearate)
fraction absorbed in airway region	20% head 50% tracheobronchial 100% pulmonary	0% head 0% tracheobronchial 100% pulmonary
fraction cleared to g.i. tract, followed by oral uptake kinetics	80% head · 20% 50% tracheobronchial · 20% 0% pulmonary	100% head · 12% 100% tracheobronchial · 12% 0% pulmonary

The result of applying these assumptions to the deposition fractions given in Table 4.5 is given in **Table 4.6**.

Table 4.6 Estimation of inhalation absorption percentage for soluble zinc compounds and for less soluble/insoluble zinc compounds

	Inhalability	Tidal volume (ml)	Breaths/ min	soluble zinc compounds (chloride and sulphate)	less soluble/insoluble zinc compounds (metal, oxide, phosphate, distearate)
Oral	off	1,100 1,700	20 23	41.1 40.4	22.4 19.4
Oronasal	off	1,100 1,700	20 23	36.1 39.2	13.4 16.8

Inhalation absorption for the soluble zinc compounds (zinc chloride and zinc sulphate) is at maximum 40%, while for the less soluble/insoluble zinc compounds (zinc metal, zinc oxide, zinc phosphate and zinc distearate) inhalation absorption is at maximum 20%. These figures will be taken forward to the risk characterisation as a reasonable worst case, because these figures are thought to cover existing differences between the different zinc industry sectors with respect to type of exercise activities (and thus breathing rate) and particle size distribution.

Dermal

Studies in animals

Skog and Wahlberg (1964) estimated the percutaneous uptake of ^{65}[Zn]-chloride by the dorsal skin of the guinea pig by monitoring the decline of radioactivity emitted by ^{65}[Zn]-chloride in at least 10 trials for each concentration tested ranging from 0.8 to 4.87 M $ZnCl_2$ (pH 1.8-6.1). It appeared that the loss of radioactivity after 5 hours was less than 1% except for the trials with the lowest pH where it might have been between 1 and 2%. The study gives too little details to be used for risk assessment.

ZnO, zinc omadine, zinc sulphate and zinc undecylenate (131 Ci/mole of $^{65}Zn^{2+}$) were used for topical application on shaved skin on the back of rabbits. Each application consisted of 2.5 mg Zn-compound containing 5 μCi $^{65}Zn^{2+}$. Two animals received one application on four skin areas left of the spine, while the four skin areas on the right side received two applications, the second one 24 hours after the first one. The rabbits were killed 6 and 24 hours after the second application. One rabbit served as control animal.

No significant differences were found in the amount and location of $^{65}Zn^{2+}$ in skin treated with 4 different zinc compounds. High concentrations of $^{65}Zn^{2+}$ were observed in the cortical and cutical zones of the hair shaft, being the highest in the keratogenous zone. Accumulation of $^{65}Zn^{2+}$ in epidermis was very low but heavy in the subdermal muscle layer. Since no different rates of absorption and concentrations of zinc compounds with different oil/water solubility, pH, and molecular weight were seen, it was suggested that the major mode of $^{65}Zn^{2+}$ uptake in skin is by diffusion through the hair follicles due to the heavy localization of $^{65}Zn^{2+}$ primarily in the hair shaft and hair follicles. According to Kapur et al. (1974) this emphasizes that chemical differences in the compounds may not play a very important role in the skin uptake of $^{65}Zn^{2+}$. No data were given on systemic absorption.

The dermal absorption of $^{65}Zn^{2+}$ from $ZnCl_2$ and ZnO was studied by applying the zinc preparations under occlusion on the shaven, but intact skin on the back of male Sprague Dawley rats (Hallmans and Lidén, 1979). The zinc absorption, being the ration between ^{65}Zn-activity in the carcass, liver and gastrointestinal tract, and the ^{65}Zn-activity in carcass, liver, gastrointestinal tract, skin and bandage, was reported to range from 1.6 to 6.1%. It should be noted that the higher percentages (3.6 to 6.1%) were achieved after application of $ZnCl_2$ in acidic solution (pH = 1). Less acidic solutions with $ZnCl_2$ or with ZnO resulted in a dermal absorption of less than 2%. In this study only the absorption into the body, excluding the skin, was determined. No data were available as to the effect of zinc chloride solutions with pH = 1 on dermal integrity.

Topical application of zinc chloride in an oil vehicle to pregnant Sprague Dawley rats, which were fed a zinc-deficient diet for 24 hours, increased the plasma concentration of zinc cations to normal or slightly above normal levels (Keen and Hurley, 1977). The absorbed fraction was not determined so it can be concluded that dermal absorption is possible but no quantification can be given.

Agren et al. (1991) showed that application of zinc oxide dressings (containing 250 µg Zn^{2+}/cm^2) to rats for 48 hours with full-thickness skin excision resulted in a 12% delivery of zinc ions from the dressing to each wound, while application of zinc sulphate dressings (containing 66 µg Zn^{2+}/cm^2) resulted in a 65% delivery of ions to each wound. The data suggest that the application of zinc oxide resulted in sustained delivery of zinc ions causing constant wound-tissue zinc cation levels due to its slow dissociation rate, while the more water soluble zinc sulphate delivers zinc ions more rapidly to the wound fluid with subsequent rapid transferral into the blood.

Studies in humans

There are no quantitative data which indicate that zinc (cations) can be absorbed through the intact skin, but absorption was reported through damaged or burned skin (EHC, 1996).

An increase in serum Zn^{2+} levels was observed in 8 patients suffering from second and third degree burns, who were treated with adhesive zinc-tape (ca. 7.5 g ZnO/100 g dry weight). The maximum value (up to 28.3 µmol/litre) was reached within 3-18 days during treatment. It is noted that the absorption through intact skin cannot be assessed based on this study with burn patients (Hallmans, 1977).

The systemic absorption from topical application of 40% zinc oxide ointment (with petrolatum) was investigated by Derry et al. (1983) in healthy subjects and in patients receiving total parenteral nutrition (TPN) for a minimum of 3 days prior to the start of the experiment. TPN is known to result in zinc deficiency (mean decrease 6.6 µg/dl/week), and the longer the period of TPN without zinc supplementation, the greater the decrease in serum zinc concentration.

Healthy volunteers: In a controlled, cross-over study (on two separate days, one week apart) 6 healthy subjects received a topical application of 100 g of the 40% zinc oxide ointment or 60 g of control ointment (100% white petrolatum base) to the chest, upper legs and lower legs (exposed skin area: not specified; occlusion: not specified) for 3 hours. Each subject fasted for 12 hours before treatment started (only water *ad libitum*). During the study no food or water was consumed. Blood samples were taken after the 12 hr-fast (baseline value), and at 1, 2 and 3 hours after the start of the topical application. Mean serum Zn^{2+} concentrations at these time points were 107.3, 116.1, 105.3 and 112.6 µg/dl for the zinc ointment and 115.2, 103.5, 105.5 and 110.5 for the control ointment, respectively. Normal serum zinc concentrations were considered to be in the range of 68 to 136 µg/dl. An increase in serum zinc over the baseline value was observed in 4/6 subjects. In 3 of them, the rise was most pronounced after 1 hour. In 2/6 no increase was observed throughout the treatment. Overall, there was a mean serum Zn^{2+} increase of 8.8 µg/dl over baseline 1 hr after application. This represented an 8.2% rise in serum zinc, which however was not statistically significant.

Patients: 6 Patients received (under occlusion) a topical application of 15 g of the 40% zinc oxide ointment onto the upper legs (10·15 cm) once daily for 8 consecutive days. Blood samples were taken before treatment (baseline value), at 4, 6 and 8 days (just prior to application), and at day 10. The mean baseline level of the patients (88.6 µg/dl) differed significantly from the mean baseline level of the healthy subjects. The mean zinc concentration in the 3 patients that completed the study remained relatively stable over the 10-day period (78-93 µg/dl).

It can be concluded that topical applications of 40% zinc oxide ointment did not result in a significant increase in serum zinc concentration in healthy human subjects over a 3-hour period nor in TPN-patients over 10 days.

Remark: It is theorised by the authors that after topical application zinc is locally absorbed and stored in the hair follicles where it is relatively unavailable for immediate systemic absorption in subjects with normal serum zinc concentrations. In subjects that are hypozincemic, there is absorption from the storage depot at a rate sufficient to prevent a decline in serum zinc concentration. It is agreed with the authors that the 3-hour sampling time in normal subjects may have been of insufficient length to allow for appreciable systemic absorption from the storage depot.

When ZnO-mediated occlusive dressings (25% w/w; 4·5 cm) were applied to the lower arm of 10 healthy volunteers for 48 hours it appeared that the mean release rate of zinc to normal skin was 5 µg/cm^2/hour. After treatment of 5 other volunteers with the ZnO dressings for 48 hours the zinc content was significantly increased in the epidermis and the accumulated blister fluid (as a model for percutaneous absorption suction blisters were used). It should be noted, however, that the zinc penetration was enhanced during the formation of blisters, indicating that the barrier function was impaired (Agren, 1990).

In another study of Agren (1991) five human volunteers were exposed to different occlusive ZnO dressings (with hydrocolloid vehicle or gum rosin). After 48 hours, suction blisters on treated skin were raised and Zn^{2+} concentration in blister fluid was determined. Furthermore, the Zn^{2+} concentration in the stratum corneum (10 successive tape strippings) was determined. The absorbed amount cannot be determined from the data presented but it appeared that the vehicle is an important factor for Zn^{2+} penetration.

In vitro studies

Pirot et al. (1996a) studied the dermal absorption of zinc 2-pyrrolidone 5-carboxylate, ZnO and $ZnSO_4$ (16 mg formulation/cm^2; 0.02–5.62% Zn^{2+}) in different formulations (3 emulsions and 2 ointments) using human abdominal skin. The receptor medium was 0.9% NaCl. After application for 72 hours, the skin was washed and stripped twice. The percutaneous absorption was determined as a percentage of the applied dose found in receptor medium and cutaneous bioavailability. It never exceeded 2%. The percentages for zinc from ointments containing ZnO and $ZnSO_4$ were 0.36% and 0.34%, respectively. The percutaneous absorption of zinc from the emulsion containing zinc 2-pyrrolidone 5-carboxylate was 1.60% of the applied dose. Furthermore the experiment showed a vehicle effect on absorption.

Pirot et al. (1996b) studied the dermal absorption of $ZnSO_4$ and $ZnCl_2$ (20 mg formulation/cm^2) in petrolatum and hydrophilic gels using human breast or abdominal skin. The receptor medium was isotonic saline. After application for 72 hours, the skin was washed and the epidermis was removed from the dermis. The result of the study was that the absorption was low, whatever vehicle was used.

The use of the data generated by Pirot et al. (1996a, 1996b) is limited because in these studies:

- the integrity of the membranes was not assessed,
- it is not clear whether or not the skin was occluded,
- cutaneous bioavailability might be underestimated in the first study due to double stripping,
- in the second study, absorption is based on Zn in fresh dermis and receptor fluid, the fresh epidermis is not included.

Industry initiated an *in vitro* testing programme on two representative zinc compounds (zinc oxide and zinc sulphate) for percutaneous absorption (Grötsch, 1999). In this study, a solution of $ZnSO_4$ monohydrate and a suspension of ZnO, each at a concentration of 40 mg/ml in water, were tested for cutaneous penetration and absorption through pig skin *in vitro*. Skin preparations measuring 1 mm in thickness with stratum corneum, stratum germinativum and blood-vessel-containing parts of the dermis were obtained from pigs using a modified dermatome.

In two independent experiments for each compound seven skin preparations were mounted in Teflon flow-through diffusion chambers which were continuously rinsed with physiological receptor fluid (0.9% NaCl in aqua bidest with antibiotics). After an integrity check using the marker substance caffeine, each of the test formulations were applied to six skins at a dose of 1 mg/cm^2 for 8 hours without occlusion, and subsequently washed off with a neutral shampoo. After 0, 2, 4, 6, 8, 16, 24, 40, 48, 64 and 72 hours, the cutaneous permeation was determined by quantifying zinc with atomic absorption spectroscopic analysis (detection limit: 10 ng/ml) in the receptor fluid. The experiment was stopped at 72 hours. Furthermore, zinc was analysed in the skin preparations and the rinsing fluids. In addition, blanks were measured in an unloaded control chamber. Results are summarised in **Table 4.7**.

Table 4.7 Dermal absorption of Zn (% of dose) through pig skin *in vitro* within 72 hours [a)]

	$ZnSO_4$	ZnO
Receptor fluid	0.3%	0.03%
Horny layer	1.3%	12.3%
Residual skin	0%	2.6%
Potentially absorbed dose	1.6%	14.9%

a) Corrected for background levels of zinc in receptor fluid and skin

Total recoveries of applied zinc in both experiments ranged from 82.0 to 109.6%. The results of analysis of the receptor fluid used and of the blank chambers without topical application of zinc compounds indicated that both the receptor fluid and porcine skin contain an intrinsic level of zinc. The amounts of zinc detected in receptor fluid and different layers of the skin were therefore corrected for background levels.

The authors concluded that dermal penetration of zinc was below 1% based on the cumulative amount recovered from the receptor fluid at 72 hours. However, the amount retained in the skin should be regarded as being absorbed because it may become available at a later stage. Hence, the rapporteur concludes that the dermal absorption of zinc from a solution of zinc sulphate monohydrate and a suspension of zinc oxide in this *in vitro* system may amount to 1.6% and 14.9%, respectively.

4.1.2.2.2 Distribution

Inhalation

No data available.

Dermal

No data available.

Oral

Studies in animals

The highest levels of radioactivity were found in the small intestine followed by the kidney, liver and large intestine six hours after a single oral administration of 0.1 µCi of $^{65}Zn^{2+}$ as zinc chloride to Wistar rats. Smaller amounts were found in the lungs and spleen. 14 Days after the administration, highest levels of radioactivity could be found in the hair, testicles, liver and large intestines (Kossakowski and Grosicki, 1983*(r)*).

Organs with high zinc concentrations (ranging from 20 to 60 mg/kg fresh weight) are liver, gut, kidney, skin, lung, brain, heart and pancreas (Bentley and Grubb, 1991*(r)*; He et al., 1991*(r)*; Llobet et al., 1988). High concentrations of zinc were also detected in the retina and in sperm (Bentley and Grubb, 1991*(r)*).

Studies in humans

After absorption from the gastrointestinal tract, Zn^{2+} is bound in plasma primarily to albumin and then transported to the liver and subsequently throughout the body.

The normal plasma zinc concentration is ca. 1 mg/l, the total zinc content of the human body (70 kg) is in the range of 1.5-2 g (ATSDR, 1994).

Zinc is found in all tissues and tissue fluids and it is a cofactor in over 200 enzyme systems. In humans, the major part of total body zinc is found in muscle and bone, approximately 60% and 30%, respectively (Wastney et al., 1986*(r)*). Under normal conditions, the highest zinc concentrations/kg tissue are found in bone, hair and prostate (Cleven et al., 1993).

The distribution of zinc in humans appears to some degree to be influenced by age. The zinc concentrations increase in the liver, pancreas and prostate and decrease in the uterus and aorta with age. Levels in kidneys and heart peak at appr. 40-50 years of age and then decline. Levels in the aorta decline after 30 years of age (Schroeder et al., 1967*(r)*).

Other routes

The tissue uptake of $^{65}Zn^{2+}$ (as zinc chloride) was determined in adult male Wistar rats after intraperitoneal injection of 15 µCi $^{65}Zn^{2+}$. The liver displayed the greatest uptake for zinc ions, followed by the kidney, pancreas, spleen, ileum, lung, heart, bone, testis, blood cells, muscle and brain. Additional data on Zn^{2+} uptake by the brain indicate that the blood-brain barrier is minimally permeable to zinc cations (Pullen et al., 1990*(r)*).

Eight hours following intravenous administration of ^{65}[Zn]-chloride to rabbits, tissue levels were highest in the liver, intestine and kidney with levels being ≥ 10%/g in tissue (Lorber et al., 1970*(r)*).

4.1.2.2.3 Metabolism

Zinc is mostly bound to organic ligands rather than free in solution as a cation (Gordon et al., 1981). Zinc is found in diffusible and no diffusible forms in the blood and about 66% of the diffusible form of zinc in the plasma is freely exchangeable and loosely bound to albumin (Cousins, 1985*(r)*). A small amount of the no diffusible form of zinc is tightly bound to α_2-macroglobulin in the plasma and is not freely exchangeable with other zinc ligands. Zinc is incorporated into and dissociated from α_2-macroglobulin only in the liver (Henkin, 1974*(r)*).

4.1.2.2.4 Excretion

Inhalation

No data available.

Dermal

No data available.

Oral

Studies in animals

After a single oral dose of 86–130 µg of ^{65}Zn as $ZnCl_2$, $ZnCO_3$ or $Zn_5(OH)_8Cl_2 \cdot H_2O$, male rats eliminated ^{65}Zn from the body with a rate of about 1.7% of the absorbed dose during day 5 to 14 post dosing as determined from stool, urinary and *in vivo* whole-body gamma counting results. In male rats who received 25 mg $ZnCO_3$/kg feed or 100 mg $Zn_5(OH)_8Cl_2 \cdot H_2O$/kg feed for 14 days, the radioactivity from a subcutaneous dose of 37 kBq of $^{65}ZnCl_2$ disappeared from the body with a rate of approximately 1% during the period 5 to 14 days post dosing (Galvez-Morros et al., 1992).

Studies in humans

In humans the fecal zinc consists of unabsorbed dietary zinc and endogenous zinc from bile, pancreatic juice and other secretions. About 70-80% of the ingested amount of zinc is excreted via feces (5 to 10 mg/day depending upon the dietary zinc concentration) (Spencer et al., 1976*(r)*; Venugopal and Lucky, 1978; Reinhold et al., 1991*(r)*; Wastney et al., 1986*(r)*). In humans about 10% of the zinc amount consumed is lost via urine (appr. 200 to 600 µg zinc/day). The urinary zinc excretion appears to be sensitive to alterations in the zinc status (Babcock et al., 1982; Aamodt et al., 1982; see below).

Minor routes of zinc excretion are saliva, hair loss, mothermilk, and sweat. In tropical climates about 2-3 mg Zn^{2+}/day may be lost in sweat (Venugopal and Lucky, 1978; Rivlin, 1983*(r)*; Prasad et al., 1963*(r)*; Rossowka and Nakamoto, 1992*(r)*; Henkin et al., 1975*(r)*).

In humans with no excessive intake of zinc, the body burden halftime of absorbed radio-labelled zinc has been observed to range from 162 to 500 days. After parenteral administration of $^{65}Zn^{2+}$, halftimes ranged from 100 to 500 days (Elinder, 1986).

Payton et al. (1982) determined body retention of Zn at 7-10 days after oral administration of 92 µmol of ^{65}Zn (as $ZnCl_2$) to 16 healthy adult human volunteers. It could be demonstrated that about 10% of the initially absorbed amount of Zn was excreted during the first 10 days post dosing. In thirty other volunteers dosed with 18 to 900 µmoles of ^{65}Zn the following elimination data for the 10 to 60 days post-dosing period were obtained:

Dose group (µmoles; (mg))	Excretion rate (% of remaining Zn per day)	Biological half-live (days)
18 (1.2)	0.44	157
45 (2.9)	0.62	111
90 (5.8)	0.37	186
180 (11.6)	0.49	141
450 (29)	0.37	186
900 (58)	0.74 a)	93

a) Significantly different from the 18 µmoles group

The excretion rates for the 18 to 450 µmoles dose groups were not different, but after the 900 µmole dose elimination was significantly increased

The excretion rates for the 18 to 450 μmoles dose groups were not different, but after the 900 μmole dose elimination was significantly increased.

The effects of additional oral zinc on excretion of orally administered ^{65}Zn were studied in 50 patients with taste and smell dysfunction. The study was conducted in three phases. In the first phase all patients were studied for 21 days after receiving a single oral dose of 3-18 μCi of ^{65}Zn (~ 0.4 to 1.2 ng zinc) as $ZnCl_2$ after an overnight fast. In the second phase, which started after 21 days and continued for 290 to 440 (mean 336) days, all 50 patients received placebo. To study the effect of additional zinc intake on elimination of previously sequestered radioactivity, in the third phase of the study 14 patients continued on placebo while 36 received $ZnSO_4$ (100 mg Zn^{2+}/day) for 112 to 440 (mean 307) days. Phases two and three were a controlled clinical trial of the effects of zinc on retention of the ^{65}Zn tracer. The results from the first phase of the study are described in Section 4.1.2.2.1.

Total body retention and activity in plasma and red cells were measured for all patients throughout the study. About one-third of the absorbed radioactivity was eliminated from the body with a half-life of ca. 19 days, while after about 100 days post dosing the remainder of the absorbed dose was eliminated with a biological half-life of 380 days (i.e. phase two of the study). During the third phase patients receiving $ZnSO_4$ showed an accelerated loss of total body ^{65}Zn ($T_{1/2}$ ca. 230 days) which was significantly different ($P > 0.001$) from half-life values during placebo treatment. Accelerated loss of ^{65}Zn from the thigh was apparent immediately while that from the liver began after a mean delay of 107 days. There was no apparent effect of zinc on loss of mean ^{65}Zn activity from red blood cells (Aamodt et al., 1982).

Remark: From the study description it is not clear whether the radioactivity was administered as pure radioactive zinc chloride or whether it was diluted with unlabelled zinc chloride. As the authors stated that "patients were given 3 to 18 μCi carrier free ^{65}Zn" for the calculation of the dose of ^{65}Zn in terms of nanogram zinc, it has been assumed that all zinc administered was in fact ^{65}Zn.

In ten patients from the Aamodt et al. 1982 study (see above) kinetics of ^{65}Zn were studied in more detail by Babcock et al. (1982). These patients received a fixed diet containing 8–13 mg Zn per day for 4 to 7 days before and after the single ^{65}Zn dose, followed by 290-440 (mean 336) days of non-restricted diet, followed by an intake of an additional 100 mg/day of non-radioactive zinc ion (as ZnSO4) over the next 112-440 days (mean 307). The overall kinetic parameters of these 10 patients did not differ from those of the other patients (Aamodt et al., 1982).

The authors further submitted retention-time curve data for whole body, plasma, red blood cells, liver and thigh to a multi-compartment kinetic model. From this model analysis it could be demonstrated that the increase in elimination of Zn during the third phase of the study by Aamodt et al. (1982) can be ascribed entirely to the change in two model parameters: reduction in absorption in the gastrointestinal tract (5-fold: from 43% absorption in the beginning of the study to 9% during the period in which patients were dosed with $ZnSO_4$) and to an increase in the urinary elimination rate (about 2-fold upon administration of $ZnSO_4$ during phase three of the study). Michaelis-Menten type saturation mechanisms were adequate to explain the observed parameter changes. These changes also accounted for the observed mean plasma zinc mass increase of only 37% above pre-load levels in face of an 11-fold increase in zinc intake (viz. from ca. 10 mg/day to ca. 110 mg/d) (Babcock et al., 1982).

Remark: From this model study it was estimated that the total body Zn contents of these 10 patients at the beginning of the study was 1.4 g. Babcock et al. (1982) indicated that normally the body contents of zinc is in the range of 2.1 to 2.5 g. This may indicate that the patients

studied by Babcock et al. (1982) and possibly by Aamodt et al. (1982) were somewhat deficient in total body Zn.

4.1.2.2.5 Homeostasis

Within certain limits, mammals can maintain the total body zinc and the physiologically required levels of zinc in the various tissues constant, both at low and high dietary zinc intakes. The sites of regulation of zinc metabolism are: absorption of Zn^{2+} from the gastrointestinal tract, excretion of zinc in urine, exchange of zinc with erythrocytes, release of zinc from tissue, and secretion of zinc into the gastrointestinal tract. Regulation of gastrointestinal absorption and gastrointestinal secretion probably contributes the most to zinc homeostasis. In spite of the mechanism for whole-body zinc homeostasis a regular exogenous supply of zinc is necessary to sustain the physiological requirements because of the limited exchange of zinc between tissues (Cleven et al., 1993).

It is hypothesised by Hempe and Cousins (1992*(r)*) that Zn^{2+} entering the luminal cells is associated with CRIP, a diffusible intracellular zinc carrier, and that a small amount is bound to metallothionein; however, as the luminal Zn^{2+} concentration increases, the proportion of cytosolic Zn^{2+} associated with CRIP is decreased and zinc binding to metallothionein increased. CRIP binds 40% of radiolabelled Zn^{2+} entering the intestinal cells of rats when zinc concentration is low; but only 14% when the concentration is high (Hempe and Cousins, 1992*(r)*).

Zinc is initially concentrated in the liver after ingestion, and is subsequently distributed throughout the body. When plasma zinc levels are high, liver metallothionein synthesis is stimulated, which facilitates the retention of zinc by hepatocytes (Richards and Cousins, 1975*(r)*).

4.1.2.2.6 Conclusion on toxicokinetics, metabolism and distribution

Several data were provided on the toxicokinetics of zinc chloride. Data on other zinc compounds have also been used, as the basic assumption is made that after intake all zinc compounds (including metallic zinc) are changed (at least in part) to the ionic species and that it is this zinc cation that is the determining factor for the biological activities of the zinc compounds.

Within certain limits, the total body zinc as well as the physiologically required levels of zinc in the various tissues can be maintained, both at low and high dietary zinc intake. Regulation of gastrointestinal absorption and gastrointestinal secretion probably contributes the most to zinc homeostasis. In spite of this a regular exogenous supply of zinc is necessary to sustain the physiological requirements because of the limited exchange of zinc between tissues.

The Zn^{2+} absorption process in the intestines includes both passive diffusion and a carrier-mediated process. The absorption can be influenced by several factors such as ligands in the diet and the zinc status.

Persons with adequate nutritional levels absorb 20-30% and animals 40-50%. However, persons that are Zn-deficient absorb more, while persons with excessive Zn intake absorb less. For risk assessment, for the more soluble zinc compounds (chloride, sulphate) the lower bound of the absorption range at adequate nutritional levels is taken (i.e. 20%). For zinc oxide it has been shown that bioavailability is about 60% of that for soluble zinc salts, corresponding to 12-18%.

For zinc metal, zinc phosphate and zinc distearate no bioavailability data were present. As these forms have limited solubility in diluted acids (stomach) comparable to zinc oxide, for the less soluble zinc compounds (oxide, phosphate, distearate, metal) an oral absorption value of 12% will be taken for risk assessment.

In situations of exposure excess (e.g. in case of high dermal or inhalation exposure at the workplace) the oral uptake of zinc compounds will probably be less than the values taken for risk assessment (20% and 12%). However, as this reduction in uptake is not quantifiable, also for excess exposure situations the same oral absorption values will be applied. Some justification for this approach can be found in the observation that for intake levels differing by a factor of 10, uptake levels vary maximally by a factor of two.

Quantitative data on the absorption of zinc following inhalation exposure (especially relevant in occupational settings) are not available. Some animal data suggest that pulmonary absorption is possible. In animal studies on zinc oxide retention in the lungs half-life values of 14 and 6.3 hours were reported for dissolution. As the absorption of inhaled zinc depends on the particle size and the deposition of these particles, data were provided on the particle size distribution of zinc aerosol in three different industry sectors. When analysing the particle size distribution data with a multiple path particle deposition (MPPDep) model, it appeared that for zinc aerosols the largest part of the deposition takes place in the head region and much less in the tracheobronchial and pulmonary region. Although most of the material deposited in the head and tracheobronchial region is rapidly translocated to the gastrointestinal tract, a part will also be absorbed locally. Based on data for local absorption of radionuclides in the different airway regions, it is assumed that local absorption for the soluble zinc compounds will amount to 20, 50 and 100% of the material deposited in head, tracheobronchial and pulmonary region, respectively. For the less soluble/insoluble zinc compounds negligible absorption is assumed for head and tracheobronchial region and 100% absorption for the pulmonary region. The remaining part of the material deposited in the different airway regions will be cleared to the gastrointestinal tract where it will follow oral uptake kinetics, hence the oral absorption figures can be applied. Applying the above mentioned assumptions to the deposition fractions as determined by the MPPDep model, inhalation absorption for the soluble zinc compounds (zinc chloride and zinc sulphate) is at maximum 40%, while for the less soluble/insoluble zinc compounds (zinc metal, zinc oxide, zinc phosphate and zinc distearate) inhalation absorption is at maximum 20%. These figures will be taken forward to the risk characterisation as a reasonable worst case, because these figures are thought to cover existing differences between the different zinc industry sectors with respect to type of exercise activities (and thus breathing rate) and particle size distribution.

Adequate quantitative data on the absorption of zinc following dermal exposure (relevant in both occupational and consumer settings) are not available. The human data presented are not considered valid, mainly since either wounded skin was investigated, or suction blisters were raised, impairing the intactness of the skin. Dermal absorption through the intact skin seems to be small (< 2%), based on the results of the *in vivo* animals studies as well as the *in vitro* studies, but unfortunately shortcomings were noted in all *in vivo* studies and none of these studies can be used quantitatively. As for the *in vitro* studies, it is clear that the % in receptor medium generally gives an underestimation of the % systemically available in *in vivo* studies. Therefore, the amount detected in the skin should be included as being absorbed by default. This 'potentially absorbed dose' more closely resembles the dose becoming systemically available *in vivo*.

Zinc bound to or in the skin may become systemically available at a later stage. This can be concluded from results in TPN patients, in which an expected decrease in serum zinc levels with

time was counteracted by dermal absorption of zinc to result in steady serum zinc levels. Unfortunately, only 3 of the 6 patients completed the 10-day study period. There are no adequate human data available to evaluate the release of zinc from normal skin following single or repeated dermal exposure, as either blood was sampled for a too short period of time (3 hours; Derry et al., 1983) or the skin was damaged (Agren, 1990, 1991; Hallmans, 1977). Therefore, it can be concluded that following single or repeated dermal exposure zinc can be taken up by the skin, whereas the relevance of this skin depot cannot be judged based on the available data. For example, it is not studied how a large artificial zinc depot in the skin will affect the uptake or homeostasis of other essential ions (e.g. Cu). However, the total database available indicates that skin-bound zinc may not become systemically available in a way that it results in high peak levels of zinc in serum, but rather in a more gradual way. Given the efficient homeostatic mechanisms of mammals to maintain the total body zinc and the physiologically required levels of zinc in the various tissues constant, the anticipated slow release of zinc from the skin is not expected to disturb the homeostatic zinc balance of the body. By expert judgement, based on the aforementioned considerations, the default for dermal absorption of solutions or suspensions of zinc or zinc compounds is therefore chosen to be 2%. Based on the physical appearance, for dust exposure to zinc or zinc compounds a 10-fold lower default value of 0.2% is chosen in the risk assessment.

Zinc is distributed to all tissues and tissue fluids and it is a cofactor in over 200 enzyme systems.

Zinc is primarily excreted via feces, but can also be excreted via urine, saliva, hair loss, sweat and mothermilk.

4.1.2.3 Acute toxicity

4.1.2.3.1 Studies in animals

Several studies with zinc chloride have been carried out in mice and rats by different routes of exposure. These studies are summarised in **Table 4.8**.

Table 4.8 Acute toxicity

Acute toxicity	Species	Protocol	Results	Reference
Oral	mouse (m)	other	LD_{50} = 1,260 mg $ZnCl_2$/kg bw	Domingo et al. (1988)
	rat (m)	other	LD_{50} = 1,100 mg $ZnCl_2$/kg bw	Domingo et al. (1988)
Inhalation	rat (f)	other	LC_{50} = (10 min) ≤ 1,975 mg $ZnCl_2/m^3$	Karlsson et al. (1986)
Intraperitoneal	mouse (m)	other	LD_{50} = 91 mg $ZnCl_2$/kg bw	Domingo et al. (1988)
	rat (m)	other	LD_{50} = 58 mg $ZnCl_2$/kg bw	Domingo et al. (1988)

Domingo et al. (1988) studied the acute toxicity in male Sprague Dawley rats and male Swiss mice, both after oral and intraperitoneal exposure. A preliminary screening was carried out with small groups of 3 animals of each species. Thereafter ten animals in each group were used and observed for 14 days. Oral doses were given intragastrically. Solution concentrations were adjusted to body weight and given at pH between 6.0 and 7.0. Majority of deaths for both species and ways of administration were observed within the first 24 hours. Signs of toxicity before death after oral or intraperitoneal administration included miosis, conjuctivitis, decreased food

and water consumption, haemorrhage and haematosis in the tail. The oral LD_{50} was 1,260 and 1,100 mg/lg bw for mice and rats, respectively. It must be noted that in this study also other zinc compounds have been tested for acute toxicity and that in the description of the clinical signs no distinction was made for the different zinc compounds.

It is concluded that zinc chloride is harmful after acute oral exposure.

In the 10-min inhalation study in female Sprague Dawley rats (Karlsson et al., 1986) analytical grade zinc chloride aerosol (generated from solutions of $ZnCl_2$ in water; droplets with MMAD of 2.3-2.6 μm) was tested, as well as a pyrotechnical mixture (smoke screen) containing zinc chloride and hexachloroethane (which is not of relevance here). With analytical grade zinc chloride aerosol no signs of irritation during or shortly after exposure were seen but signs of respiratory distress developed gradually. Zinc chloride aerosol was lethal to rats at concentrations from 940 mg Zn^{2+}/m^3 (≈1,975 mg $ZnCl_2/m^3$), the animals died within 3 days after exposure. Microscopic findings in the lungs included atelectasis, hyperaemia, haemorrhages and oedema, however without a clear-cut dose-response relationship. The LC_{50} of ≤ 1,975 mg/m^3 in this study with very small particle size droplets (which might not reflect exposure to inhalable dust under normal conditions) indicates that zinc chloride is toxic by inhalation. However, because of the short duration of the exposure period (10 min.) it cannot be excluded that zinc chloride might even be very toxic by this route.

No data were available on the acute dermal toxicity of zinc chloride.

Additional single exposure studies

Male Wistar rats (5/group) were given intratracheally a dose of 2.5 mg $ZnCl_2$/kg bw and were killed 3, 14, 28 or 35 days after dosing. Within 3 hours after dosing all rats were subdued and showed respiratory distress. Histology showed alveolitis around the major bronchi, most severe on day 3 after treatment. A change from macrophage to lymphocyte infiltration was seen in the damaged areas at day 14, without evidence of fibrosis. At 28 days, early alveolar thickening with increased interstitial reticulin deposition was observed, and at 35 days these changes had amounted to mature, discrete areas of parenchymal scarring (Brown et al., 1990).

After intratracheal administration of $ZnCl_2$ to male Wistar rats at dose levels of 0, 0.25, 0.5, 1, 2, 4 or 5 mg/kg bw no histological effects on the lung tissue were seen up to 0.5 mg $ZnCl_2$/kg bw. At higher dose levels, a dose-related intra-alveolar oedema was observed (Richards et al., 1989*(r)*).

Exposure of male Wistar rats to a dose of 2.5 mg $ZnCl_2$/kg bw by instillation caused oedema of the lung and a tenfold increase in the level of alveolar surface protein within 6 hours of treatment. The pulmonary oedema was most severe between 6 hours and 3 days after exposure, with more than half of the rats showing oedema (Richards et al., 1989*(r)*).

4.1.2.3.2 Studies in humans

Oral intake of "one tablespoon" by a 16-month old boy (McKinney et al., 1994; 1995) or 'about three ounces' of a zinc chloride solution (soldering flux) by a 24-year old male (Chobanian, 1981) led to local caustic effects, nausea, vomiting, abdominal pain, hyperamylasemia and lethargy.

Inhalation exposure to concentrations between 0.07 and 0.4 mg/m^3 zinc chloride fume for 30 minutes failed to elicit sensory effects. In the same study, an average concentration of 4.8 mg/m^3 over a 30-minute period caused mild, transient irritation of the respiratory tract in bearing manufacture workers (Ferry, 1966*(r);* 1974*(r)*).

At exposure to 40 mg/m^3 zinc chloride aerosol a metallic taste was detected. Experimental exposure to zinc chloride for 2 minutes resulted in slight nausea and some cough at 80 mg/m^3 in the majority of human subjects, whereas at 120 mg/m^3 irritation of the nose, throat and chest were noted (Cullumbine, 1957*(r)*). Exposure to 4,800 mg/m^3 for 30 minutes induced pulmonary effects. There are no further data available (Lewis, 1992).

Accidental exposure to zinc chloride fume resulted in intoxications (Evans, 1945; Hjortsø et al., 1988; Homma et al., 1992; Johnson and Stonehill, 1961; Macaulay and Mant, 1964; Matarese and Matthews, 1986; Milliken et al., 1963; Pare and Sandler, 1954; Schenker et al., 1981), but quantitative data are lacking except for one study (Johnson and Stonehill, 1961), where the concentration was 4,075 mg/m^3 (duration of exposure not indicated). After inhalation, shortness of breath, pain in the throat, acute inflammation of the respiratory tract, cyanosis, bronchopneumonia, painful cough with sputum, chest pain and tightness, nausea and vomiting, headache, pulmonary oedema and fibrosis, acute respiratory insufficiency was experienced more or less in increasing order of seriousness. In several cases the symptoms receded one or two hours after exposure, but occasionally aggravated a few hours up to 2 weeks later. In a few cases the high exposure concentration was fatal.

4.1.2.3.3 Conclusion on acute toxicity

Based on the data submitted zinc chloride is harmful after acute oral exposure. According to EC criteria (Council Directive 67/548/EEC) zinc chloride needs to be classified as harmful if swallowed (Xn; R22).

The data submitted indicate that zinc chloride can be toxic or even very toxic after acute inhalatory exposure. It is realised that exposure to the small particle size droplets used in the animal study might not be representative for inhalatory exposure under normal conditions where no particle sizes below 100 µm are expected to occur. However, particle size may not be that relevant, given the effects seen on lung tissue after intratracheal dosing. Hence, classification as toxic or very toxic by inhalation would be justified. In addition, classification as irritant to the respiratory system seems appropriate, based on airway irritation symptoms observed in laboratory animals as well as humans.

4.1.2.4 Irritation

Studies in animals

Skin

0.5 ml $ZnCl_2$ (1% solution in deionised water) was applied on the dorsal skin (5 cm²) for 5 consecutive days in open patch tests with mice, rabbits and guinea pigs and in an occlusive test with rabbits. In the open patch test 4/4 rabbits and 6/6 mice had severe irritancy and 3/8 guinea pigs had moderate irritancy (scoring from slight (+) to severe (+++)). In the occlusive patch test 4/4 rabbits had severe irritancy. The severe skin effects in the open patch tests were characterised

by parakeratosis, hyperkeratosis and inflammatory changes in the epidermis and superficial dermis and acanthosis of the follicular epithelia. In the occlusive patch test similar, but more severe, effects were observed, and in addition erythema and ulceration (Lansdown, 1991).

Zinc chloride has been classified as corrosive to the skin according to the EC criteria.

Respiratory tract

In single exposure studies with rats (see Section 4.1.2.3.1) signs of respiratory distress and oedema were reported.

Eye

Data on eye irritation are not submitted. Although this is a base set requirement this is considered acceptable since zinc chloride is a corrosive substance and accordingly labelled.

Studies in humans

See Section 4.1.2.3.2 for respiratory irritation in humans.

Corneal oedema developed when concentrated zinc chloride was accidentally splashed into three eyes of two patients. Some permanent corneal scarring resulted. Recovery required 6 to 28 weeks. The patient who had also splashes in his nasal passages lost all sense of smell permanently, in spite of medical treatment (Houle and Grant, 1973).

Conclusion on irritation

After repeated exposure to zinc chloride, severe damage to the skin was observed. Despite the fact that the study was not entirely according to the guidelines, the severity of the observed effects probably justifies classification and labelling (R34) as mentioned in Appendix A.

4.1.2.5 Corrosivity

Zinc chloride can be considered as a corrosive substance (see Section 4.1.2.4).

4.1.2.6 Sensitisation

No data are available regarding the sensitising effects of zinc chloride in humans as well as in animals. However, a derogation was accepted that given the corrosive properties of zinc chloride and the fact that for the Cl-ion no sensitisation can be expected, sensitisation data from another soluble zinc compound (i.e. zinc sulphate) could be used in the assessment of a sensitising potential for zinc chloride. Zinc sulphate was not a skin sensitiser in animals (see Risk assessment report on zinc sulphate).

Conclusion on sensitisation

Data on skin sensitisation are not available for zinc chloride. However, based on the accepted derogation and the fact that zinc sulphate is not a skin sensitiser, it is consequently concluded that zinc chloride is not likely to have skin sensitising potential, and therefore does not need to be classified/labelled.

No data are available on the potential for respiratory sensitisation.

4.1.2.7 Repeated dose toxicity

4.1.2.7.1 Studies in animals

Limited data were provided on the repeated dose toxicity of zinc chloride. Data on other zinc compounds have been used, as the basic assumption is made that after intake all zinc compounds (including metallic zinc) are changed (at least in part) to the ionic species and that it is this zinc cation that is the determining factor for the biological activities of the zinc compounds (see Section 4.1.2.1).

The section is divided in two subsections. Under "Relevant studies for risk assessment" more or less guideline repeated dose studies were evaluated that allowed the establishment of a N(L)OAEL. The subsection "Additional studies" comprises studies with animals other than standard laboratory animals, special investigations into specific parameters, limitedly reported studies etc.

Relevant studies for risk assessment

See **Table 4.9**.

Table 4.9 Repeated dose toxicity

Repeated dose toxicity	Species	Protocol	Results	mg Zn^{2+}/ kg bw	Reference
Oral	mouse	other, but comparable with guideline study: 300 to 30,000 mg $ZnSO_4$•7 H_2O /kg feed daily via diet for 13 weeks	NOAEL 3,000 mg/kg feed At 30,000 mg/kg feed: heamatological and biochemical effects were observed. Gross pathology and histopathology showed changes in kidney, thyroid, gastrointestinal tract and pancreas.	NOAEL: 104 LOAEL: 1,107	Maita et al. (1981)
	rat	other, but comparable with guideline study: 300 to 30,000 mg $ZnSO_4$•7 H_2O/kg feed daily via diet for 13 weeks	NOAEL 3,000 mg/kg feed At 30,000 mg/kg feed: hematologic effects and pancreatic damage.	NOAEL: 53.5 LOAEL: 564	Maita et al. (1981)
	rat	According to OECD 408: up to 1% Zn-mono glycerolate via diet (~ 31.52 to 758.73 mg/kg bw) for 13 weeks	NOAEL 31.52 mg/kg bw At 0.2% (≈ 127.52 mg/kg bw): effects on pancreas, spleen and clinical chemical parameters	NOAEL: 13.26 LOAEL: 53.65	Edwards and Buckley (1995)

Oral exposure

- Zinc sulphate

ICR mice (12/sex/group) were given daily doses of 300, 3,000 or 30,000 mg $ZnSO_4 \cdot 7\ H_2O$/kg feed (equivalent to 42.7/46.4, 458/479 and 4,927/4,878 mg/kg bw for males/females, respectively) during 13 weeks. A control group was included. At the highest dose level 4 males and 1 female were found dead or killed in extremis. Histological findings of these animals revealed impairment of the urinary tract and regressive changes in the exocrine gland of the pancreas. Only the high dose animals showed moderately lower haematocrit (males: from 42% in controls to 29% in high dose animals; females: from 44% in controls to 31% in high dose animals) and haemoglobin concentrations (males and females: 14 to 10 g/dl). The leucocyte counts of high dose males were moderately decreased (lymphocytes 70 to 60%; monocytes 5.3 to 4.9%). Total protein, glucose and cholesterol were reduced and alkaline phosphatase and urea nitrogen were increased in high dose animals. High dose females showed reduced ALAT and increased calcium levels, ASAT was increased in high dose males. Absolute and relative (in parentheses) thyroid weights of males were increased from 3.3 mg (0.007%) in control animals to 4.2 mg (0.0011%) in the highest dose group. Kidney weights of females were also increased from 0.42 g (0.93%) in controls to 0.53 g (1.62%) at the highest dose. Gross pathology and histopathology showed changes in kidneys, thyroids, pancreas (degeneration/necrosis of acinar cells, clarification of nucleoli), gastrointestinal tract, and spleen. No effects were found on the reproductive organs (i.e. ovaries, testes, accessory sex organs). The NOAEL in this study is 458 and 479 mg $ZnSO_4 \cdot 7\ H_2O$/kg bw for males and females, respectively (≈ 104 mg Zn^{2+}/kg bw) (Maita et al., 1981).

Wistar rats (12/sex/group) were given daily doses of 300, 3,000 or 30,000 mg $ZnSO_4 \cdot 7\ H_2O$/kg feed (equivalent to 23.2/24.5, 234/243, and 2,514/2,486 mg/kg bw for males/females, respectively) during 13 weeks. A control group was included. At the highest dose level a moderate reduction in leucocyte counts was seen in both sexes (males: from $7.3 \cdot 10^3$/mm^3 in controls to $4.7 \cdot 10^3$/mm^3 in high dose animals; females: from $4.5 \cdot 10^3$/mm^3 in controls to $3.3 \cdot 10^3$/mm^3 in high dose animals). Compared to controls, males also showed slightly decreased haematocrit (42 to 40%), decreased total protein (5.2 to 4.4 g/dl) and cholesterol values (96 to 62 mg/dl). Absolute and relative (in parentheses) liver weights were decreased in the high dose males (from 16.1 g (3.55%) in controls to 11.9 g (3.20%) at the highest dose). Absolute kidney weights were decreased in high dose males (2.29 g vs. 2.93 g in controls). Histopathology showed pancreatic damage (degeneration, necrosis of acinar cells, clarification of centroacinar cells and interstitial fibrosis) in high dose animals. No effects were found on the reproductive organs (i.e. ovaries, testes, accessory sex organs). The NOAEL is 234 and 243 mg $ZnSO_4 \cdot 7\ H_2O$/kg bw for males and females, respectively (≈ 53.5 mg Zn^{2+}/kg bw) (Maita et al., 1981).

- Zinc monoglycerolate

Groups of 20 male and 20 female Sprague Dawley rats were fed zinc monoglycerolate at dietary levels of 0, 0.05 or 0.2% (equal to 0, 31.52 or 127.52 mg/kg for males and 0, 35.78 or 145.91 mg/kg bw for females, respectively) for a period of 13 weeks in a study performed according to OECD 408. A similar group was fed 1% (equal to 719 and 805 mg/kg bw/day for males and females, respectively) of zinc monoglycerolate up to day 58 of the study when a deterioration in their clinical condition (poor physical health and reduced food intake) necessitated reducing the dietary level to 0.5% (equal to 632 and 759 mg/kg bw/day for males and females, respectively). However, as no improvement occurred these rats were killed on humane grounds on day 64 of the study. These rats developed hypocupremia manifested as a hypochromic microcytic regenerative type anaemia (low haemoglobin and haematocrit,

decreased MCV and MCH, and increased MCHC, red blood cell and reticulocyte count). Enlargement of the mesenteric lymph nodes and slight pitting of the surface of the kidneys were noted. Severe pancreatic degeneration and pathological changes in the spleen, kidneys, incisors, eyes and bones were observed. The testes of all males showed hypoplasia of the seminiferous tubules to a varying degree and in addition the prostate and seminal vesicles showed hypoplasia. In all but one female the uterus was hypoplastic.

All other rats survived to the end of the 13 weeks treatment. At a dietary level of 0.2% increases in plasma ALAT, alkaline phosphatase and creatine kinase were observed in males and in plasma creatine kinase in females. Total plasma cholesterol was reduced in both males and females. The changes were statistically significant but small in absolute terms. No changes in haematological parameters were seen at 0.05 and 0.2%. A dose related reduction in the quantity of abdominal fat was noted in male rats at 0.05 and 0.2%. Enlargement of the mesenteric lymph nodes was apparent in 6 out of 20 rats fed 0.2% and in one male fed 0.05%. Microscopic examination showed a reduction in the number of trabeculae in the metaphysis of the tibia of 5 male and 3 female rats fed 0.2%, 4 males and 1 female had a similar reduction in the metaphysis of the femur. Pancreatic cell necrosis was seen in both sexes at 0.2% and a slight, but statistically not significant increase could be noted at 0.05% (3 males and 1 female). This pancreatic cell necrosis was seen also in 1 control male. A reduction in the number of pigmentated macrophages in the red pulp of the spleen was observed in both sexes at 0.2% and a marginal reduction was also seen in males at 0.05%. In the animals given 0.05 and 0.2% no effects were found on the reproductive organs.

Since the pancreatic cell necrosis, being without statistical significance at 0.05%, was also apparent in 1 control male and because the reduction in pigmented macrophages in the spleen was only marginal at 0.05% without any haematological changes the dose level of 0.05%, is considered as a NOAEL. This dose level is equal to 31.52 or 35.78 mg zinc monoglycerolate/kg bw for males and females, respectively, so the NOAEL in this study is 31.52 mg/kg bw (≈ 13.26 mg Zn^{2+}/kg bw) (Edwards and Buckley, 1995).

Inhalation exposure

No proper inhalation toxicity data are available.

Dermal exposure

No dermal toxicity data are available.

Additional studies

Oral exposure

- Zinc sulphate

A group of 150 C3H mice was given daily doses of 0.5 g $ZnSO_4$ (unspecified)/l drinking (≈ 100 mg $ZnSO_4$/kg bw/day; ≈ 22.6 mg Zn^{2+}/kg bw in case heptahydrate was used) water for 1 year. A 2-month post observation period and a control group were included. At monthly intervals 5 control and 5 test animals were investigated for plasma zinc, glucose and insulin, and for zinc in skin, liver and spleen. Histology, histochemistry and microscopy were performed on adrenals and pancreas, and on adenohypophysis only microscopy. The animals remained healthy throughout the study. Hypertrophy of the adrenal glands (cellular enlargement) and hypertrophy and vacuolisation of pancreatic islets and fasciculata cells in adrenal cortex from month 3

onwards. Changes indicating hyperactivity in the anterior pituitary were noted, such as increased cell size of all cell types in the pituitary. All the other parameters remained the same during the study. The study was undertaken to further investigate the effects of supplemental zinc on endocrine glands and correlate these effects with any change in body zinc levels produced (Aughey et al., 1977).

Mink (3/sex/group) were given diets supplemented with 0, 500, 1,000 or 1,500 mg/kg feed zinc sulphate for 144 days. Zinc concentrations in liver, pancreas and kidney increased with increasing zinc content in the diet. No histological lesions were found in these organs (Aulerich et al., 1991*(r)*).

- Zinc chloride

Wistar rats (2 months, 16 males and 14 females) were given 0.12 mg Zn^{2+}/ml drinking water (equivalent to 12 mg Zn^{2+}/kg bw; 25 mg $ZnCl_2$/kg bw) for 4 consecutive weeks. A control group was included. The body weights of exposed males and food and water intakes of both exposed sexes decreased. A statistically significant decrease in Hb level (85% of control value) and erythrocyte count was reported in the peripheral blood of treated rats. An increased leucocyte count, due to increased lymphocyte numbers was noted in treated males. No inhibition of erythropoiesis in the bone marrow was found. No more details were given in this limited study performed to investigate the effect of simultaneous oral administration of zinc and vanadium and therefore it cannot be used for risk assessment (Zaporowska and Wasilewski, 1992).

- Zinc oxide

Special studies were conducted to examine the morphological and histoenzymatic changes of the brain. Twelve Wistar rats were given daily doses of 100 mg ZnO (ca. 600 mg ZnO/kg bw ≈ 480 mg Zn^{2+}/kg bw) intragastrically for 10 consecutive days. A control group was included. After 10 days the rats were sacrificed and the brains were examined for morphological and histoenzymatic changes.

Morphological changes included degenerative changes of neurocytes, accompanied with moderate proliferation of the oligodendroglia and glial proliferation in the white matter. Furthermore endothelial oedema was observed in the small arterial and capillary walls. Histoenzymatic changes included decreased activities of ACP (acid phosphatase), ATPase (adenosinetriphosphatase), AChE (acetylcholine esterase), and BuTJ (Butyrylthiocholine esterase). The activities of TTPase (thiamine pyrophosphatase) and NSE (non specific esterase) were increased. No details on quantitative aspects of enzymatic changes were given. No change was seen in the alkaline phosphatase. The authors indicated that observed morphological and histoenzymatic changes were unspecific, undistinctive and most likely reversible (Kozik et al., 1980). Examination of the neurosecretory function of the hypothalamus and the hypophysis in these animals showed an increased neurosecretion in cells of the supraoptic and paraventricular nucleus of the hypothalamus along with a declined neurosecretion in the hypophysis and an enhanced release of antidiuretic hormone in the neurohypophysis (Kozik et al., 1981). It is not clear whether these observations represent an adverse effect of zinc on the brain or whether they are secondary to changes somewhere else in the body.

Four groups of ferrets (3-5/group) were given 0, 500, 1,500 or 3,000 mg zinc oxide/kg feed (equivalent to be 0, 81.3, 243.8 or 487.5 mg ZnO/kg bw, respectively. At the highest dose level (487.5 mg ZnO/kg bw) all animals (3) were killed in extremis within 13 days. Macroscopic examination showed pale mucous membranes, dark coloured fluid in the stomach, blood in the intestines, orange coloured liver and enlarged kidneys showing diffuse necrosis, haemorrhages in

the intestine and a severe macrocytic hypochromic anaemia. Histology showed nephrosis and extramedullary haematopoesis in the spleen. At the mid dose level of 243.8 mg ZnO/kg bw the animals (4) were killed on day 7, 14 and 21 (1/2 in extremis) showing poor condition. Macroscopy showed pale livers with fatty infiltration and enlarged kidneys. Histology was comparable with the highest dose group. The haemogram showed macrocytic hypochromic anaemia, increased reticulocytes and leucocytosis.

At the lowest dose level (81.3 mg ZnO/kg bw) the animals (3) were killed on day 48, 138 and 191, respectively. No clinical signs of toxicity or pathological changes were seen, apart from an extramedullary heamatopoesis in the spleen (Straube et al., 1980).

Ellis et al. (1984) conducted a 14-day and a 49-day feeding study in 3 different breeds of sheep that were receiving feed containing 31 mg Zn^{2+}/kg feed. The sheep received additional amounts of Zn^{2+} (from ZnO) at dose levels of 261 and 731 (14-day study) or 731 and 1,431 mg Zn^{2+}/kg feed (49-day study). No effects were seen after 261 mg Zn^{2+}/kg feed. In all other groups pancreatic lesions were seen.

Administration of 240 mg Zinc (as ZnO)/kg bw for 3 times/week during 4 weeks to 42 castrated sheep resulted in an increased incidence of pancreatic lesions (Smith and Embling, 1993*(r)*).

Inhalation exposure

- Zinc oxide

Male Hartley guinea pigs were exposed to 0, 2.3, 5.9 or 12.1 mg/m^3 of ZnO (as ultrafine particles with an average diameter of 0.05 μm) 3 hours a day for 1, 2 or 3 consecutive nose-only exposures. Three animals from each group were examined after each exposure period, were sacrificed and lung tissues were microscopically examined, and the pulmonary lavage fluid was also examined.

Exposure to 12.1 mg/m^3 increased the number of nucleated cells in lavage fluid. Exposures to 5.9 and 12.1 mg ZnO/m^3 were associated with increased protein, neutrophils, and activities beta-glucuronidase, acid phosphatase, alkaline phosphatase, lactate dehydrogenase, and angiotensin-converting enzyme. The increases were dose dependent and were detectable after the second exposure, and generally increased after the third exposure. Significant morphologic damage characterised by centriacinar inflammation in the lung was seen at 5.9 and 12.1 mg/m^3. Minimal changes in neutrophils and activities of lactate dehydrogenase and alkaline phosphatase were seen in the pulmonary fluid at the lowest dose level of 2.3 mg/m^3 after 3 exposures but no morphologic changes were observed at this dose level. Based on these results 2.3 mg ZnO/m^3 is considered as a marginal LOAEL in this study (Conner et al., 1988).

Male Hartley guinea pigs were exposed to 6 mg/m^3 of ultrafine ZnO (average diameter of 0.05 μm) for 3 hours a day for 1 to 5 days by nose-only exposure. A control group was included. After each exposure 3 animals were sacrificed and lung tissues were microscopically examined. After first, second and third exposure 3 additional animals were sacrificed and their pulmonary lavage fluid was examined. ZnO-exposure increased the total cell count, neutrophils, protein and the enzyme activities of angiotensin converting enzymes, Acid phosphatase, alkaline phosphatase, and β-glucoronidase. Furthermore a dose-related centriacinar inflammation was seen after second exposure (Conner et al., 1986).

Male Hartley guinea pigs were exposed to 0, 2.7 or 7 mg ultrafine (0.05 μm in diameter) ZnO/m^3 3 hours a day for 5 days. Lung function measurements were performed every day after exposure

in 5-8 animals. After the last exposure the animals were sacrificed. At the highest exposure level a gradual decrease in total lung capacity (18%) and vital capacity (22%) was seen during the exposure period. At day 4 the carbon monoxide diffusing capacity dropped to below 30% of the control level. Wet-lung weights were increased with 29%, indicating the presence of edema. Exposures up to 2.7 mg ZnO/m^3 did not alter any parameters measured (Lam et al., 1988).

Male Hartley guinea pigs (73) were exposed (nose-only) 3 hours a day for 6 days to 5 mg ZnO/m^3 (0.05 µm in diameter). A group of 53 animals served as control group. Lung function tests (in 38 animals) were performed and the respiratory tract of the animals was morphologically examined 1, 24, 48 and 72 hours after the last exposure. Furthermore epithelial permeability (5 animals at 1 and 24 hours) and DNA synthesis in epithelial cells (5 animals at 24, 48 and 72 hours) were determined.

Vital and functional residual capacity, alveolar volume and carbon monoxide diffusing capacity were all decreased and did not return to normal values 72 hours after the last exposure. Lung weights were elevated due to inflammation, still present at 72 hours after last exposure (Lam et al., 1985).

240 Female Wistar rats (80/group) were exposed by inhalation to 15 mg ZnO/m^3 for 1 hour, 4 hours or 8 hours a day for 5 days a week. 20 Animals/group were sacrificed after 14, 28, 56, and 84 days and their lungs were examined for zinc content.

It appeared that the highest daily exposure time resulted in the highest dry lung weights, independent of the duration of the experiment, while the zinc content remained almost constant. The absolute and relative (relative to dried weights of lung tissue) zinc content in the lungs was influenced by the duration of the experiment. After 84 days of exposure the zinc content was significantly higher compared to 14 days exposure, independent of the duration of the daily exposure (Dinslage-Schlünz and Rosmanith, 1976).

4.1.2.7.2 Studies in humans

All relevant oral human data concerning metallic zinc and zinc compounds are reported in this section.

Dietary levels were not measured in all of the studies reported here. According to a Total Diet Study performed by the US Food and Drug Administration (FDA) over the period 1982 to 1986, adult males (25-35 years of age) consumed an average of 16.4 mg Zn^{2+}/day. Adult females (25-30 years of age) consumed an average of 9.72 mg Zn^{2+}/day (Pennington, 1989).

Zinc sulphate

In a double-blind cross-over trial 47 healthy volunteers (26 females and 21 men) ingested zinc sulphate capsules containing 220 mg zinc sulphate, three times a day with each meal (resulting in a total daily dose of 150 mg Zn^{2+} i.e. ≈ 2.1 and 2.5 mg Zn^{2+}/kg bw /day for males and females, respectively) for six weeks. Plasma zinc and copper levels, plasma cholesterol, plasma low-density-lipoprotein (LDL) and high-density-lipoprotein (HDL) cholesterol, serum ceruloplasmin and erythrocyte superoxide dismutase (ESOD) were determined. In 84% of the women and 18% of the men symptoms were reported which included headaches, nausea, vomiting, loss of appetite and abdominal cramps. The study authors reported that the gastric discomfort went together with lower body weights and taking the capsules with small meals (breakfast or morning tea) or no food. Plasma zinc levels rose significantly in both men and women (36% and

57%, respectively). Plasma copper levels did not change significantly. Total plasma cholesterol and HDL were unchanged in both sexes. In females the LDL cholesterol decreased significantly from 2.38 to 2.17 mmol/l. In females a decrease was also found in serum ceruloplasmin (13% reduction) and in ESOD (ca. 20% reduction) (Samman and Roberts, 1987, 1988).

Hooper et al. (1980) examined the effect of oral zinc administration on human lipoprotein values. Twelve healthy adult men were given oral doses of 440 mg zinc sulphate/day (≈ 2.3 mg Zn^{2+}/kg bw/day in the form of two zinc sulphate capsules containing 220 mg zinc sulphate (80 mg elemental zinc per capsule resulting in a total daily dose of 160 mg Zn^{2+}), each capsule to be eaten with a main meal for 35 days. Fasting lipid levels were determined on a weekly basis and continued two weeks after zinc supplementation stopped, with a final determination at 16 weeks after start of the experiment. HDL cholesterol levels were decreased by 25% at the 7^{th} week, but had returned to baseline levels at 16 weeks. Total serum cholesterol, triglyceride and LDL cholesterol levels were not changed.

Remark: There is a discrepancy between the dosimetric data in the Samman and Roberts study (1987/1988) as compared to the Hooper et al. study (1980). In the first study, a daily dose of 660 mg zinc sulphate was declared to be equivalent to a dose of 150 mg Zn^{2+} per day, while in the second study a daily dose of 440 mg zinc sulphate was stated to have resulted in a daily dose of 160 mg Zn^{2+}. This discrepancy can only be explained by assuming that in the Samman and Roberts study zinc sulphate was administered in the form of the heptahydrate, while in the Hooper et al. study the monohydrate has been used. As this is not clearly stated in either of the two studies, the dosimetric data which are presented here are the same as those given in the respective publications.

Chandra (1984) examined the effect of zinc on immune response and serum lipoproteins. Zinc sulphate was administered twice daily to 11 adult men for a total (extra) intake of 300 mg elemental zinc/day (≈ 4.3 mg Zn^{2+}/kg bw/day). Dietary zinc intake amounted to ca 11 mg/person/day. None of the subjects showed evidence of any untoward side effects. There was a significant increase in serum zinc levels and reduction in lymphocyte stimulating response to PHA after 4 and 6 weeks of treatment. A slight increase in LDL was observed together with a significant reduced level of HDL cholesterol.

In two studies the side effects of zinc administration as a medication in the treatment chronic leg ulcers was investigated:

- in a double-blind trial, 13 humans received 200 mg zinc sulphate (± 135 mg Zn^{2+}) three times a day for 18 weeks, while 14 humans received a placebo. No signs of nephrotoxicity associated with the zinc treatment were reported, but the study was not sufficiently documented to fully appreciate the relevance of its result (Hallbook and Lanner, 1972),
- in a study of Greaves and Skillen (1970) no indications for haematotoxicity, hepatotoxicity or nephrotoxicity, as determined by several clinical biochemical and haematological parameters, were seen in 18 humans after administration of 220 mg zinc sulphate (± 150 mg Zn^{2+}) 3 times a day for 16-26 weeks.

Zinc gluconate

In a 12-week double blind study Black et al. (1988) administered zinc gluconate tablets to 2 groups of healthy male volunteers for 12 weeks at doses equivalent to 50 or 75 mg zinc/kg bw/day (≈ 0.71 and 1.1 mg Zn^{2+}/kg bw/day). A control group received a placebo tablet. No changes in serum

cholesterol, triglyceride, and LDL and very-low-density-lipoprotein (VLDL) cholesterol levels were observed.

In a 10-week single-blind oral study by Yadrick et al. (1989) 9 healthy female volunteers were given 50 mg Zn^{2+} (as zinc gluconate)/day (≈ 0.83 mg Zn^{2+}/kg bw/day) and 9 other healthy female volunteers were given 50 mg Zn^{2+} (as zinc gluconate)/day plus 50 mg Fe^{2+} (as ferrous sulphate monohydrate) in two daily doses via their diet to investigate the effect of zinc supplementation on iron, copper and zinc status. The subjects (assumed mean body weight of 60 kg) served as their own controls. In both groups the erythrocyte superoxide dismutase (ESOD) activity was significantly reduced with 47% after 10 weeks. In the zinc supplemented group, after 10 weeks significant decreases in haematocrit (by 4%) and serum ferritin levels (with 23%) were seen, whereas the haemoglobin levels were unchanged. In the zinc+iron supplemented group, serum ferritin levels were significantly increased (by 25%), whereas the haematocrit and haemoglobin levels were unchanged. The ceruloplasmin concentration, another indicator for copper status besides ESOD, was not altered in both groups, but the serum zinc concentration was significantly increased. The NOAEL in this study is less than 0.83 mg Zn^{2+}/kg bw.

A significant decrease of 15% in ESOD activity was reported by Fischer et al. (1984) who administered 50 mg Zn^{2+} (as zinc gluconate)/day (≈ 0.71 mg Zn^{2+} /kg bw) divided in two daily doses to 13 healthy young men (assumed mean body weight of 70 kg) for 6 weeks in a double-blind study design. The other two indices of copper status, i.e. ceruloplasmin activity and plasma copper levels were not changed compared to the controls at 2, 4 or 6 weeks, but the serum zinc levels were significantly increased from 2 weeks of supplementation onwards. Serum zinc showed a significant inverse correlation with ESOD activity at 6 weeks.

The study of Yadrick et al. (1989) as well as the study of Fischer et al. (1984) showed several limitations such as:

- the short duration of the studies and the small number of subjects,
- the absence of a placebo-controlled group in the Yadrick study. However, all subjects served as their own controls,
- the lack of information on the dietary levels of zinc (and iron and copper); the diets were not controlled,
- the absence of physical or medical examination.

Over the course of the past several years, industry has been sponsoring a series of human volunteer studies in conjunction with the Grand Forks Human Nutrition Research Center of the U.S. Department of Agriculture. These studies, recently completed, have been evaluating impacts of moderate zinc deficiency and moderate zinc excess as a function of intake levels for mineral nutrients such as copper. This because extremely high amounts of zinc have been shown to interfere with the uptake and metabolism of copper, and it was questioned if moderately high intakes of zinc would also be antagonistic to copper metabolism. The studies are anticipated to demonstrate the fashion in which subtle biochemical alterations associated with zinc deficiency and excess will vary as a function of copper status, and to evaluate exposure biomarkers with potential applications for monitoring zinc status. The results of two of these studies are now available for public circulation (see studies by Davis et al., and Milne et al., below).

In a controlled metabolic unit study by Davis et al. (2000), various indicators of zinc status were measured in 25 healthy postmenopausal women (mean age 64.9 years) to evaluate the usefulness of these indicators as a marker for the functional assessment of zinc status in humans. The

subjects were kept under close supervision for 200 days, divided into two 90-day dietary periods, each preceded by a 10-day equilibration period. The subjects received a daily diet with a total energy content of 8.4 MJ (or 2,000 kcal). In the equilibration periods the subjects received a diet containing 2 mg copper/day and 9 mg zinc/day. For the 90-day dietary periods the subjects were randomly divided into two groups, one group (n = 12) was fed a low copper diet (1 mg Cu/day) and the other group (n = 13) a high copper diet (3 mg Cu/day). In the first 90-day dietary period both groups received no zinc supplement (low zinc; 3 mg Zn/day), while in the second 90-day dietary period both groups received a zinc supplement of 50 mg per day (high zinc; 53 mg Zn/day). Zinc was supplemented as zinc gluconate and copper as cupric sulphate. Blood samples were taken (after overnight fasting for 12 hours) during each of the equilibration periods and one to twice monthly during the dietary periods, and analysed for various zinc-status indicators.

Zinc concentrations in erythrocytes and erythrocyte membranes, plasma and erythrocyte membrane alkaline phosphatase activities, and erythrocyte membrane 5'nucleotidase activity did not change statistically significantly with the different dietary treatments.

Zinc supplementation significantly increased plasma zinc concentrations and activities of mononuclear 5'nucleotidase and extracellular superoxide dismutase ($P < 0.0001$). For all three indicators the effect of zinc supplementation was dependent on the copper intake although this was not statistically significant for plasma zinc. In case of mononuclear 5'nucleotidase activity, the difference caused by zinc supplementation was apparent when subjects were fed high dietary copper (92% change) but not when they were fed low dietary copper (5% change). The effects for plasma zinc and for extracellular superoxide dismutase activity were more apparent when subjects were fed low dietary copper (35 vs. 22% and 21 vs. 8% change, respectively). Independent of copper intake, zinc supplementation caused relatively small increases in free thyroxine (7-8%) and triiodothyronine (7-9%) concentrations, platelet zinc concentrations (10-13%) and bone specific alkaline phosphatase activity (18%) ($0.002 < P < 0.08$). The levels of the affected indicators were elevated from the equilibration values at all dietary treatments, with the exception of extracellular superoxide dismutase activity at low copper/low zinc, mononuclear 5'nucleotidase activity at low copper/low zinc, low copper/high zinc and high copper/low zinc, and thyroxine and triiodothyronine concentrations at all dietary treatments. Plasma zinc concentrations were within the normal range for healthy adults (10.7-18.4 μmol/L) throughout the low zinc period, but during zinc supplementation 8 out of 23 subjects had plasma zinc concentrations > 18.4 μmol/L.

Decreased activities upon zinc supplementation were found for plasma 5'nucleotidase activity ($P < 0.0001$), thyroid stimulating hormone concentrations ($P < 0.07$) and erythrocyte superoxide dismutase activity (ESOD; not statistically significant). For these three indicators the decrease was somewhat more apparent when fed high dietary copper (28 vs. 29%, 5 vs. 9%, and 3 vs. 5%, respectively). However, for plasma 5'nucleotidase and ESOD the levels at high dietary copper were higher than at low dietary copper (only at high copper/low zinc the levels were elevated from equilibration values). For thyroid stimulating hormone the levels were depressed from equilibration values at all dietary treatments. Limited data suggested that zinc supplementation in combination with low dietary copper depresses amyloid precursor protein expression in platelets (Davis et al., 2000).

Remark: Data from two volunteers fed low copper diets were not included: they had to be supplemented with dietary copper because of significant changes in their electrocardiograms.

In the same dietary experiment as described by Davis et al. (2000; see above), also other parameters (i.e. copper-status and iron-status indicators) were investigated to study the effect of

moderately excessive and deficient intakes of zinc on copper metabolism and utilization in humans fed low and luxuriant amounts of copper (Milne et al., 2001). For that purpose, urine and faeces were collected during the last 78 days of each 90-day dietary period and copper and zinc were determined (in faeces in 6-day composite samples). Once weekly blood was sampled (after overnight fasting for 12 hours), and blood samples were analysed for various copper-status and iron-status indicators.

Women fed low copper were in negative copper balance. Zinc intake (low or high) did not alter this. Women fed high copper were put into negative copper balance by low zinc. Upon transition to high zinc, women fed high copper came into positive copper balance, which apparently was the result of a lower amount of dietary copper lost in the faeces; urinary copper was not affected.

The zinc balance reflected dietary zinc intake (more positive with increased zinc intake) and was not significantly affected by copper intake.

Copper-status indicators were variably affected by dietary treatment. The concentrations of serum ceruloplasmin (enzymatically determined), HDL and VLDL cholesterol, triglycerides and red blood cell zinc did not change statistically significantly with the different dietary treatments.

Independent of zinc intake, plasma copper concentrations were significantly lower on low dietary copper than on high dietary copper ($P < 0.07$). Although plasma copper concentrations were depressed from equilibration values at all dietary treatments, the depression was less for high than for low dietary copper ($P < 0.03$).

Independent of copper intake, zinc supplementation caused increases in the concentrations of serum ceruloplasmin (immunochemically determined; 4-8%, $P < 0.05$) and plasma zinc (19-32%, $P < 0.0001$) and in platelet cytochrome c oxidase activity (on a platelet number basis; 19-27%, $P < 0.0007$), and decreases in the concentrations of red blood cell copper (8-16%, $P < 0.0008$) and whole blood glutathione (8-12%, $P < 0.009$) and in the activities of specific ceruloplasmin (defined as the ratio between enzymatic and immunoreactive ceruloplasmin; 8-11%, $P < 0.0003$) and erythrocyte glutathione peroxidase (11-15%, $P < 0.002$). The levels of these indicators were elevated from equilibration values at all dietary treatments, with the exception of serum immunoreactive ceruloplasmin concentration (reduced at all dietary treatments), platelet cytochrome c oxidase activity (reduced at high copper/low zinc), specific ceruloplasmin activity and whole blood glutathione concentration (essentially at equilibration values at low copper/high zinc and high copper/high zinc), and red blood cell copper concentration (essentially at equilibration value at low copper/low zinc and reduced at low copper/high zinc).

Zinc supplementation significantly decreased ESOD activity (5-7%, $P < 0.03$) as well as the concentrations of total cholesterol (3-4%, $P < 0.005$) and LDL cholesterol (2-6%, $P < 0.003$), but not by much. The effect on ESOD was dependent on copper intake ($P < 0.0001$): compared to equilibration values, ESOD activity decreased on low copper but increased on high copper. Total cholesterol and LDL cholesterol concentrations were significantly higher on low dietary copper than on high dietary copper ($P < 0.02$ and $P < 0.03$, respectively). This suggests a dependency on copper intake, but it should be noted that women fed low copper had higher equilibration values for both indicators than women fed high copper.

The authors state that measured indicators of iron status (serum iron, haemoglobin, haematocrit and percent transferrin saturation) were unaffected by dietary treatment (no data presented), with the exception of haemoglobin, which was lower on high zinc than on low zinc in both the low

and high copper groups. The drop in haemoglobin occurred especially during the last month of zinc supplementation, possibly due to the frequent blood sampling.

Remark: Data from another two volunteers (one on a low copper diet and one on a high copper diet) were not included, because they were using an adhesive containing extremely high amounts of zinc for their false teeth.

Remarks on the Grand Forks study, reported by Davis et al. (2000) and Milne et al. (2001)

1. From personal communication with the authors it appears that for ESOD activity the initial equilibration values varied markedly between individuals, and that for women who were assigned to the low copper group ESOD activity was substantially higher than for those assigned to the high copper group. This implicates that for this indicator, the assignment of the subjects to the two groups was suboptimal, which might also be the case for other indicators.
2. The frequent blood sampling (an average of no more than 235 ml per month was drawn) might have compromised the physiology of the subjects (as was suggested for haemoglobin).
3. The subjects served as their own controls: values upon both treatments (i.e. low and high zinc administration) were compared with values upon first equilibration. However, as the second treatment is not independent of the first treatment, the study design is not optimal.

In the human studies described above, the effects of high or moderately high dietary zinc on several indicators known to be associated with copper status have been investigated. These indicators included plasma zinc and copper concentrations, cholesterol and lipoprotein cholesterol concentrations, and several enzyme activities (e.g. ESOD and ceruloplasmin). Effects of zinc on the latter are thought to precede changes in plasma and tissue levels of the elements, given the primary role of zinc as a component of different enzymes. In humans supplemented with zinc, plasma zinc concentration was elevated, while plasma copper concentration was not affected. In the earlier studies by Samman and Roberts (1987/1988), Yadrick et al. (1989) and Fischer et al. (1984) reductions in ESOD activity were found upon zinc supplementation. This was thought to be associated with copper deficiency, as was the reduction in ceruloplasmin activity found by Samman and Roberts (1987/1988). In the more recent and more sophisticated studies by Davis et al. (2000) and Milne et al. (2001), however, only very small reductions in ESOD activity were observed that did not correlate with changes in copper balance. The clinical significance of this ESOD reduction can be doubted, because the findings in these studies on more specific copper deprivation signs (decreased serum ceruloplasmin and platelet cytochrome c oxidase) indicate that sub-optimal intake of zinc was more effective than a moderately high intake of zinc in inducing changes associated with a decreased copper status in postmenopausal women. It might also be that the small decrease in ESOD activity with high zinc intake was not caused by an interference with copper metabolism, but was more reflective of reduced oxidative stress given the serum glutathione and erythrocyte glutathione peroxidase findings. However, one can only conclude from the Grand Forks studies (Davis et al., 2000; Milne et al., 2001) that very subtle changes were induced by the different dietary treatments.

From various studies (e.g. Fischer et al., 1990; Barnett and King, 1995; Verhagen et al., 1996 and Puscas et al., 1999) it can be concluded that ESOD activities in healthy human volunteers may show a coefficient of variation of at least 10 to 20%. Although it is impossible to compare the absolute ESOD activities as reported by these authors to those from the Grand Forks studies, due to methodological differences, the relative changes in activities as reported by Davis et al. (2000) and Milne et al. (2001) can be compared to the coefficient of variation of ESOD activity, showing that the changes found in the Grand Forks studies are within the range of natural

variation. In addition, Fischer et al. (1990) have demonstrated that in a large group of male and female human volunteers of different ages, ceruloplasmin and serum copper levels were highly correlated, but that no correlation between serum copper concentration and ESOD could be established. ESOD activity was independent of sex, age, pre-post menopausal status, estrogen use (including that in post-menopausal women), smoking or drinking habits, or level of physical exercise.

The general function of ESOD, also within red blood cells, is to catalyze the dismutation of superoxide anion radicals to hydrogen peroxide and oxygen, thus preventing damage of cell constituents and structures by this radical intermediate generated during the oxygen transport function. Concentrations of superoxide anion radicals are in the order of 0.01–0.001 nmol/l under non-pathological conditions. Hydrogen peroxide, on the other hand, is destroyed by catalase being present in high amounts within erythrocytes resulting in concentrations between 1 and 100 nmol/l. According to our knowledge there are only few measured data available showing a direct relationship between changes of intracellular concentrations of free radicals and tissue damage.

Assuming that there is a considerable reduction of the ESOD activity then higher concentration of superoxide radical anions should occur in red blood cells which may lead to destructive effects. Such effects should be detectable, e.g. by changes in haematological parameters (e.g. increased hemolysis, decreased number of erythrocytes, increase in reticulocytes). However, such findings have not been observed in any study. In the Grand Forks studies (Milne et al., 2001) hematocrit, serum iron, and transferrin saturation were unaffected by a dose of 50 mg Zn^{2+}/day leading to a 3-7% reduction of ESOD activity. Yadrick et al. (1989) reported a 47% decrease of ESOD activity after giving 50 mg Zn^{2+}/day over 10 weeks. However, this decrease of ESOD is accompanied by a small decrease in hematocit value.

The subtle changes in clinical-biochemical parameters, as reported in the Grand Forks studies, are hardly indicative for zinc-induced perturbations of the copper homeostasis. These biochemical changes do not lead to detectable deterioration of red blood cell functioning. Therefore, these changes are also of marginal biological significance, if any. Hence, it is concluded that in women supplemented with zinc, a dose of 50 mg Zn^{2+}/day is a NOAEL.

4.1.2.7.3 Conclusion on repeated dose toxicity

Limited data were provided on the repeated dose toxicity of zinc chloride. Data on other zinc compounds have been used, based on the assumption that after intake the biological activities of the zinc compounds are determined by the zinc cation.

Studies in animals

No repeated dose toxicity studies after dermal exposure are available in animals.

After inhalation exposure mainly studies of short duration (3-6 days) are available. In a 3-day inhalation study with guinea pigs a concentration of 2.3 mg ultrafine ZnO/m^3 (3 hours/day) was a marginal LOAEL, showing changes in neutrophils and activities of lactate dehydrogenase and alkaline phosphatase in the pulmonary fluid. At higher concentrations increased protein concentration, neutrophils, and enzyme activities in lung lavage fluids were seen, together with significant centriacinar inflammation of the pulmonary tissue. A dose of 2.7 mg ultrafine ZnO/m^3 (3 hours/day for 5 days) did not alter the lung function parameters in guinea pigs but at 7 mg ultrafine ZnO/m^3 (3 hours/day for 5 days) or at 5 mg ultrafine ZnO/m^3 (3 hours/day for

6 days) a gradual decrease in total lung capacity, vital capacity and reduction of the carbon monoxide diffusing capacity were seen in combination with inflammatory changes and edema. The relevance of the findings in studies with ultra-fine zinc oxide fumes is unclear with respect to commercial grade zinc oxide, as the latter is of much larger particle size and can have different toxicological characteristics.

In two oral 13-week studies with zinc sulphate (one with rats and one with mice) and an oral 13-week study with zinc monoglycerolate in rats, the lowest oral NOAEL was found in the study with zinc monoglycerolate. This overall NOAEL is 31.52 mg zinc monoglycerolate/kg bw (≈ 13.26 mg Zn^{2+}/kg bw). At higher doses the most important effects the rats developed were hypocupremia, and significant changes in the pancreas (focal acinar degeneration and necrosis) and the spleen (decreased number of pigmented macrophages). It should be noted that in the studies with zinc sulphate mice and rats could be maintained up to 13 weeks on a diet containing 30,000 mg $ZnSO_4 \cdot 7\ H_2O$/kg feed (equivalent to 6,794 mg Zn^{2+}/kg feed), while in the 13-week study with zinc monoglycerolate with rats 1.0% zinc monoglycerolate in the diet (equivalent to 4,420 mg Zn^{2+}/kg feed) was so detrimental that animals had to be killed on humane grounds after 9 weeks.

Studies in humans

Upon supplementing men and women with 150 mg Zn^{2+}/day (as zinc sulphate capsules), women appeared to be more sensitive than men to the effects of high zinc intake: clinical signs such as headache, nausea and gastric discomfort were more frequent among women, and women but not men had decreased activities of serum ceruloplasmin and ESOD. In some earlier oral studies in which humans were supplemented with moderately high amounts of zinc (50 mg Zn^{2+}/day), a reduction in ESOD activity was also observed and again women appeared to be more sensitive to this effect. Hence, a reduction in ESOD was thought to be a sensitive indicator of copper status. However, in more recent and more sophisticated studies using the same dose level, ESOD was only marginally reduced (without a correlation with changes in copper balance), while findings on more specific copper deprivation signs (decreased serum ceruloplasmin and platelet cytochrome c oxidase) indicated that a sub-optimal intake of zinc was more effective than a moderately high intake of zinc in inducing changes associated with a decreased copper status in postmenopausal women. Given this, and degree of the observed ESOD reduction in comparison to the natural variability in its activity, the zinc-induced decrease in ESOD activity is considered to have marginal biological significance, if any, also because it may not have been caused by an interference with copper metabolism.

Overall, it is concluded from studies in which humans were supplemented with zinc (as zinc gluconate), that women are more sensitive to the effects of high zinc intake and that a dose of 50 mg Zn^{2+}/day is a NOAEL. At the LOAEL of 150 mg Zn^{2+}/day, clinical signs and indications for disturbance of copper homeostasis have been observed. The human oral NOAEL of 50 mg Zn^{2+}/day (0.83 mg/kg bw/day) will be taken across to the risk characterisation.

4.1.2.8 Mutagenicity

Several *in vitro* and *in vivo* studies were provided on the genotoxicity of zinc chloride. Data on other zinc compounds have also been used, as the basic assumption is made that after intake all zinc compounds (including metallic zinc) are changed (at least in part) to the ionic species and that it is this zinc cation that is the determining factor for the biological activities of the zinc compounds (see Section 4.1.2.1).

The tests that are considered useful for the assessment of the genotoxicity of Zn^{2+} are summarised in **Table 4.10**.

Table 4.10 Mutagenicity data

Genetic toxicity	Species	Protocol	Results	Form	Reference
***In vitro* studies**					
Bacterial test (gene mutation)	S. typhimurium (4 strains)	Ames test; 1,000–5,000 µg/plate	negative	oxide	Crebelli et al. (1985)*
Bacterial test (gene mutation)	S. typhimurium (3 strains)	Ames test	negative	oxide	Litton Bionetics (1976)*
Bacterial test (gene mutation)	S. typhimurium (5 strains)	Ames test: with and without m.a.; 5 doses, up to 3,600 µg/plate	negative	sulphate	Gocke et al. (1981)
Bacterial test (gene mutation)	S. typhimurium (1 strain)	other: without m.a.; up to 3,000 nM/plate	negative	sulphate	Marzin and Vo Phi (1985)*
Bacterial test (gene mutation)	S. typhimurium (4 strains)	unknown	negative	chloride	Kada et al. (1980)*(r)*
Bacterial test (gene mutation)	S. typhimurium	Ames test: with and without m.a.	negative	distearate	Litton bionetics (1977)*(r)*
Bacterial test (gene mutation)	S. typhimurium (4 strains)	according to OECD guideline No. 471; 50-5,000 µg/plate; no toxicity up to 5,000 µg/plate	negative	mono-glycerolate	Jones and Gant (1994)**
Bacterial reverse mutation test	E. coli (strain WP2s (λ))	other: induction of λ prophage (adaptation of McCarroll et al., 1981); conc. 3,200 µmol/l; m.a. unknown	ambiguous (two-fold increase of λ prophage induction)	chloride	Rossman et al. (1984)
Eukaryotic assay (gene mutation)	S. cerevisiae (1 strain)	other: without m.a.; single concentration (0.1 mol/l) screening assay	weakly positive (no details given)	sulphate	Singh (1983)*
Eukaryotic assay (gene mutation)	S. cerevisiae (1 strain)	unknown: m.a. unknown; 1,000 and 5,000 ppm	negative	sulphate	Siebert et al. (1970)*
Eukaryotic assay (gene mutation)	S. cerevisiae	unknown	negative	distearate	Litton Bionetics (1977)*(r)*
Eukaryotic assay (gene mutation)	mouse lymphoma cells	unknown: with and without m.a.	positive	oxide	Cameron (1991)(*r*)
Eukaryotic assay (gene mutation)	mouse lymphoma cells	according to OECD guideline No. 476; without m.a. 1-15 µg/ml (toxic at 15 µg/ml) with m.a. 1-30 µg/ml (toxic at 30 µg/ml)	positive: without m.a. from 10 µg/ml with m.a. from 15 µg/ml	mono-glycerolate	Adams and Kirkpatrick (1994)**
Eukaryotic assay (gene mutation)	mouse lymphoma cells	unknown: without m.a.	negative	chloride	Amacher and Paillet (1980)*(r)*

Table 4.10 continued overleaf

Table 4.10 continued Mutagenicity data

Genetic toxicity	Species	Protocol	Results	Form	Reference
***In vitro* studies**					
Cytogenetic assay (SCE's)	Syrian hamster embryo cells	unknown; m.a. unknown	ambiguous	oxide	Suzuki (1987)*
Cytogenetic assay	human embryonic lung cells:WI-38	unknown: without m.a.; 0.1, 1.0 and 10 µg/plate	negative	sulphate	Litton Bionetics (1974)*
Cytogenetic assay (chromosomal aberrations)	human lymphocytes	other: m.a. unknown; 0, 30 and 300 µM (3mM toxic)	ambiguous	chloride	Deknudt and Deminatti (1978)*
Cytogenetic assay (chromosomal aberrations)	human lymphocytes	according to OECD guideline No. 473; cytotoxicity at 40 µg/ml (MI 51%), con. tested: without m.a. 5–20µg/ml, with m.a. 10–40 µg/ml	positive in the presence of m.a. at 30 and 40 µg/ml	mono-glycerolate	Akhurst and Kitching (1994)**
Cytogenetic assay (chromosomal aberrations)	human lymphocytes	other: without m.a.; 0, 20, and 200 µg/culture (2,000 µg toxic)	negative	chloride	Deknudt (1982)*
Unscheduled DNA synthesis	Syrian hamster embryo cells	unknown: without m.a.; 0.3, 1, 3, 10 and 30 µg/ml	positive ≥ 1 µg/ml	oxide	Suzuki (1987)*
Cell transformation assay	Syrian hamster embryo cells	unknown: without m.a.; 0, 1, 3 µg ZnO/ ml	positive 1 and 3 µg/ml	oxide	Suzuki (1987)*
Cell transformation assay	Syrian hamster embryo cells	unknown; up to 20 µg/ml	negative	chloride	Di Paolo and Casto (1979)*(r)*
Cell transformation assay	Syrian hamster embryo cells	unknown; 0-0.34 mM	equivocal	chloride	Casto et al. (1979)
Cell transformation assay	Syrian hamster embryo cells	unknown; 0-0.2 mM	equivocal	sulphate	Casto et al. (1979)
***In vivo* studies**					
Cytogenetic assay (chromosomal aberrations)	mouse	other: 0.5% zinc in calcium-deficient (0.03% Ca) or standard diet (1.1% Ca) for 30 days	slightly positive in case of calcium deficient diet in the survivors (0.5% Zn with poor Ca-diet resulted in 50% mortality after 30 days)	chloride	Deknudt (1982)*
Cytogenetic assay (chromosomal aberrations)	mouse	other; single i.p. injections of 0, 7.5, 10 or 15 mg $ZnCl_2$/kg bw and repeated i.p. injections every other day of 2 and 3 mg $ZnCl_2$/kg bw for 8, 16 or 24 days.	single dose study: positive; repeated dose study: positive	chloride	Gupta et al. (1991)

Table 4.10 continued overleaf

Table 4.10 continued Mutagenicity data

Genetic toxicity	Species	Protocol	Results	Form	Reference
***In vivo* studies**					
Cytogenetic assay (chromosomal aberrations)	rat	other: 5 months inhalation of 0.1 to 0.5 mg/m^3	only slight increases of chromosomal aberrations were seen; primarily hyperdiploid cells were seen.	oxide	Voroshilin et al. (1978)*
Cytogenetic assay (chromosomal aberrations)	rat	other: 2.75, 27.5 or 275 mg/kg bw by gavage once or daily for 5 consecutive days	negative	sulphate	Litton Bionetics (1974)
Micronucleus	mouse	other: i.p. 28.8, 57.5 or 86.3 mg/kg bw at 0 and 24 hours	negative	sulphate	Gocke et al. (1981)
Micronucleus	rat	other: resembling OECD guideline No. 474; 0.05%, 0.2%, and 1% in purified diet over a 13 week period	negative	mono-glycerolate	Windebank et al. (1995)**
Host-mediated assay	mouse	other: 2.75, 27.5 or 275 mg/kg bw by gavage once or daily for 5 consecutive days	weakly positive	sulphate	Litton Bionetics (1974)
Dominant lethal assay	rat	other: 2.75, 27.5 or 275 mg/kg bw by gavage once or daily for 5 consecutive days	negative	sulphate	Litton Bionetics (1974)
Drosophila SLRL test	drosophila melanogaster	other; 5 mM (in 5% saccharose) adult feeding method	negative	sulphate	Gocke et al. (1981)
Drosophila dominant lethal and SLRL test	drosophila melanogaster	unknown; 0.247 mg/ml adult feeding	negative	chloride	Carpenter and Ray (1969)*

m.a.: metabolic activation

* Although study or study documentation showed limitations (see hedset), the study is considered useful for the evaluation of the genotoxicity of zinc

** Studies on zinc monoglycerolate, submitted within the framework of the EEC Council Regulation

4.1.2.8.1 *In vitro* studies

Exposure to zinc compounds did not increase the mutation frequencies in the bacterial test systems (Gocke et al., 1981; Crebelli et al., 1985; Marzin and Vo Phi, 1985; Kada et al., 1980*(r)*; Litton Bionetics, 1976*(r)*; Jones and Gant, 1994), except for one ambiguous result with zinc chloride reported by Rossman et al. (1984).

A weakly positive and two negative results were found in eukaryotic test systems using the yeast S. cerevisiae (Singh, 1983; Siebert et al., 1970, Litton Bionetics, 1977).

A negative result (Deknudt, 1982) and a positive result (Akhurst and Kitching, 1994) were found for chromosomal aberrations in human lymphocytes. A negative (Amacher and Paillet, 1980*(r)*)

and two positive results (Cameron, 1991(*r*); Adams and Kirkpatrick, 1994) were reported in mouse lymphoma assays (gene mutations).

A negative (zinc chloride) as well as a positive (zinc oxide) result in a cell transformation assay using Syrian hamster embryo cells was reported by Di Paolo and Casto (1979*(r)*) and Suzuki (1987), respectively. Equivocal results in this assay were reported for zinc chloride and zinc sulphate, producing enhancement of cell transformation in 3/6 and 3/7 trials, respectively (Casto et al., 1979). Suzuki (1987) reported a positive UDS test and an ambiguous result with zinc oxide in an SCE test.

4.1.2.8.2 *In vivo* studies

Two reliable negative micronucleus tests were reported in mice (Gocke et al., 1981) and rats (Windebank et al., 1995).

Zinc chloride induced chromosomal aberrations in mouse bone marrow in case of an extreme calcium deficient diet. In this study C57Bl mice received during one month a normal (with 1.1% Ca) or poor calcium diet (0.03% Ca) in combination with 0.5% of zinc. After this month 50% of the animals given the poor calcium diet in combination with 0.5% zinc died. No information was given about the mortality in the other groups. Ten survivors of each group were sacrificed another month later and their bone marrow cells were studied on chromosome aberrations. In each group 500 metaphases were studied. Total cells damaged were 9 in controls with normal Ca, 10 in controls with low Ca, 14 in Zn-exposed with normal Ca, and 25 in Zn-exposed with low Ca diet (Deknudt, 1982).

Mice (5 per group) were given intraperitoneal injections of 7.5, 10 or 15 mg zinc chloride/kg bw/day. After treatment of the animals with colchicine bone marrow preparations were collected at 24 hours post dosing and 60 metaphases were studied per animal. At all doses an increase (dose-related) in chromosomal aberrations in bone marrow cells was observed as compared to the controls. Next to this, mice (5/group) were i.p. injected for 4, 8 or 12 times with 2 or 3 mg zinc chloride/kg bw every other day and the observed incidence of chromosomal aberrations was compared to the control group of the single dose study. Again an increase in incidence was found (after 4 injections only at the highest dose, at 8 and 12 injections at both doses), but the control group used is not entirely appropriate. The cauda epididymis of the animals in the single dose study was minced and sperm cells were examined. An increase in sperm head abnormalities was found, but further study details and criteria for interpretation were not provided (Gupta et al., 1991). The increase in chromosomal aberrations observed in the single dose study is considered reliable.

No chromosomal aberrations were induced when rats were given 2.75, 27.5 or 175 mg/kg bw zinc (as zinc sulphate) by gavage once or daily for 5 consecutive days (Litton Bionetics, 1974). Only a slight increase in chromosomal aberrations in rat bone marrow was reported by Voroshilin et al. (1978) after exposure to zinc oxide by inhalation. Female rats were subjected to continuous inhalation of a zinc oxide aerosol in concentrations of 0.5 and 0.1 mg/m^3 for 5 months. 200 Metaphases were studied and the total amount of cells damaged were 1.0% in controls, 4.5% in rats exposed to 0.1 mg/m^3, and 6.5% in rats exposed to 0.5 mg/m^3.

Zinc sulphate tested negative in a drosophila SLRL test (Gocke et al., 1981) and a dominant lethal assay in rats (Litton Bionetics, 1974). A drosophila dominant lethal and SLRL test with zinc chloride (Carpenter and Ray, 1969) was also negative.

A host-mediated assay with zinc sulphate appeared to be weakly positive (Litton Bionetics, 1974).

4.1.2.8.3 Conclusion on mutagenicity

Several data were provided on the genotoxicity of zinc chloride. Data on other zinc compounds have also been used, based on the assumption that after intake the biological activities of the zinc compounds are determined by the zinc cation.

The available data indicate that the genotoxicity results vary widely. Conflicting results have been found, even in the same test systems. Overall, the results of the *in vitro* tests indicate that zinc has genotoxic potential *in vitro* based on positive results in mammalian test systems for gene mutations and chromosomal aberrations and on the positive *in vitro* UDS test.

In *vivo,* increases in chromosomal aberrations were found in calcium-deficient mice exposed via the diet as well as in mice with normal calcium status when dosed intraperitoneally. In mice also negative results were obtained and even at higher intraperitoneal dose levels. Rats tested negative for chromosomal aberrations after oral dosing, either via gavage or via the diet. The positive result for chromosomal aberrations *in vitro* is considered over ruled by negative *in vivo* tests for this endpoint.

The positive sperm head abnormality test is considered sufficiently counter-balanced by two negative SLRL tests as well as two negative dominant lethal tests. Moreover, this sperm test is not adequately reported and without details on scoring criteria, interpretation of the observations is rather subjective. In addition, sperm head abnormalities are indicative rather than proof for genotoxicity.

Based on the available data there is insufficient ground to classify zinc as genotoxic. It should be noted that the potential to induce gene mutations was not adequately tested *in vivo*. However, there is no clear evidence from the available data that zinc is genotoxic *in vivo* and without a clear indication for carcinogenicity (see below) a guidance for further testing with respect to target tissue is not available.

4.1.2.9 Carcinogenicity

No adequate long-term carcinogenicity studies are available. All the information regarding the carcinogenic properties of zinc or zinc compounds is included in this section.

4.1.2.9.1 Studies in animals

Testicular teratomas were reported in early studies in poultry, birds and rats following repeated intratesticular injection of different zinc compounds, such as $ZnCl_2$ and $ZnSO_4$. No tumourogenic effects have been found when zinc was administered by intramuscular or subcutaneous injection (Léonard et al., 1986).

In a limited older study the tumour incidences in Chester Beatty mice were studied after administration of 1,000 and 5,000 ppm zinc sulphate ($ZnSO_4 \cdot 7\ H_2O$) in drinking water (equal to 4.4 and 22 g/l water; calculated to be 200 or 1,000 mg Zn^{2+}/kg bw) for 45-53 weeks. A control group was included, however concurrent controls were used after a number of animals died after

an intercurrent disease (ectromelia). The starting number of animals per group was not given. Only 22-28 mice/group survived at the end of the exposure period. Observations were limited to "thorough examinations once each week and more cursorily examinations each day", body weight measurements and at the end 'a thorough post-mortem examination' with a histological examination for lesions that were possibly neoplastic. Results were only given for incidence and types of tumours. The incidences of hepatoma, malignant lymphoma, and lung adenoma and the evidence of hyperplasia in the fore-stomach epithelium were not different between exposed and control mice. No other tumours developed (Walters and Roe, 1965).

Although no direct carcinogenic actions of dietary zinc deficiency or supplementation are known, the growth rate or frequency of transplanted and chemically induced tumours is influenced by the zinc content in the diet. Both promoting and inhibiting actions have been reported depending on the experimental conditions. Experiments with rodents suggest that cancer growth is retarded by zinc deficiency and may be promoted by large amounts of zinc intake. These effects may be explained by the fact that zinc is needed in DNA synthesis and cell replication (Deknudt and Gerber, 1979; Léonard et al., 1986).

4.1.2.9.2 Studies in humans

A cohort study of 4,802 refinery workers in nine electrolytic zinc and copper refining plants (i.e. one zinc, one copper + zinc and seven copper refineries), who had been employed between 1946 and 1975, reported slightly reduced mortality in the 1,247 workers who had been exposed to "zinc" alone (978) or in combination with "copper" (269). Employees were incorporated in the study when they had worked in the electrolytic department for at least one year. Age adjusted Standardised Mortality Ratio's were calculated on the basis of comparison with the mortality rates for the entire US population for the year 1970. Of the 1,247 workers who were exposed to "zinc" (either alone or in combination with "copper"), 88 died before the end of the follow-up. For 12 of these, the cause of death could not be retrieved. 143 workers were lost to follow-up entirely. Cancer rates were only analysed for the entire cohort of refinery workers (i.e. all 4,802 participants). An association between cancer mortality and employment in zinc and/or copper refinery was not found. However, the study does not permit to draw a conclusion about any association between cancer mortality and zinc exposure, because cancer mortality for "zinc"-workers was not analysed separately from cancer mortality for "copper"-workers (Logue et al., 1982).

Neuberger and Hollowell (1982) studied excess in lung cancer mortality associated with residence in an old-lead/zinc mining and smelting area in the US. The age and sex adjusted mortality rates were compared to state and national rates. The analysis determined that lung cancer mortality was elevated in the region. Quantification of inhabitant's exposure to zinc was not part of the study. The authors mentioned several possible causes for the increased lung cancer rates such as smoking habits, occupational exposure (e.g. in mining and associated activities) and residence. Ore contaminants were arsenic, cadmium, iron, sulphur, germanium and radioactivity. Tuberculosis and silicosis were commonly seen among the region inhabitants. From this study any conclusion on a possible association between exposure to environmental levels of lead or zinc and the increased lung cancer rate cannot be drawn.

Leitzmann et al. (2003) examined the association between supplemental zinc intake (level and duration) and prostate cancer among 46,974 US men participating in the Health Professionals Follow-Up Study. During 14 years of follow-up (from 1986 through 2000), 2,901 new cases of prostate cancer were ascertained, of which 434 cases were diagnosed as advanced cancer.

Approximately 25% of the study population used zinc supplements (24% in amounts ≤ 100 mg/day, 1% in amounts > 100 mg/day). Supplemental zinc intake at doses of up to 100 mg/day was not associated with prostate cancer risk. However, compared with non users, users with an excessively high supplemental zinc intake (> 100 mg/day) had a relative risk of advanced prostate cancer of 2.29 (95% CI 1.06 to 4.95). Increasing the duration of supplemental zinc use was unrelated to the risk of total prostate cancer. However, for chronic users (> 10 years) the relative risk of advanced prostate cancer was 2.37 (95% CI 1.42 to 3.95). According to the authors residual confounding by supplemental calcium intake or some unmeasured correlate of zinc supplement use cannot be ruled out. They also indicate that strong evidence to support a specific mechanism for the association is lacking at present, and that further exploration for the possible role of chronic zinc oversupply in prostate carcinogenesis is needed.

4.1.2.9.3 Conclusion on carcinogenicity

The available data are limited. Zinc deficiency or supplementation may influence carcinogenesis, since promoting and inhibiting actions have been reported. However, there is no clear experimental or epidemiological evidence for a direct carcinogenic action of zinc or its compounds.

4.1.2.10 Toxicity for reproduction

Limited data were provided on the reproductive toxicity of zinc chloride. Data on other zinc compounds have been used, as the basic assumption is made that after intake all zinc compounds (including metallic zinc) are changed (at least in part) to the ionic species and that it is this zinc cation that is the determining factor for the biological activities of the zinc compounds (see Section 4.1.2.1).

Zinc is necessary for normal growth and development (e.g. gene expression, metabolism of vitamins including folate, retinol) and therefore it is not surprisingly that a zinc deficiency can cause foetal damage as reported in animals (Walsh et al., 1994; ATSDR, 1994). Both human and animal data show that zinc deficiency will also lead to delayed sexual maturation and to impairment of reproductive capacity (WHO, 1996).

4.1.2.10.1 Studies in animals

Fertility

For zinc no 1- or 2-generation studies are available. However, one study is available in which some attention was paid to the effects of zinc on male fertility (Samanta and Pal, 1986), while in another study (Pal and Pal, 1987) effects on female fertility were studied. In addition, three repeated dose toxicity studies are available in which mice and rats were exposed for 13 weeks to dietary zinc. In these three studies the effects of zinc on gonads and accessory sex organs were studied.

18 Male Charles-Foster rats were exposed via diet to 4,000 mg Zn^{2+} (as anhydrous zinc sulphate)/kg feed (about 200 mg Zn^{2+}/kg bw/day) for 30-32 days before mating. 15 Males served as controls. The males were mated individually with female rats of proven fertility and sacrificed

the day after mating. There was a statistically significant difference between the number of control females that conceived (15/15) and the treated females (11/18). Zinc treatment resulted in significantly lower numbers of live birth. Increased zinc concentrations were found in the testes (not in the other reproductive organs examined) and sperm of treated males. The motility of the sperm was reduced, but the viability was unaffected (Samanta and Pal, 1986).

When 12 female Charles-Foster rats received via diet 4,000 mg Zn^{2+} (as anhydrous $ZnSO_4$)/kg feed (corresponding to 200 mg Zn^{2+}/kg bw/day) from day 1 until day 18 post coitum, only 5 females conceived versus 12 in the control group. The numbers of implantation sites per pregnant female and per mated female were both lower in the treated group. After administration of the same dose from day 21-26 prior to mating until sacrifice (day 18 post coitum), 14 out of 15 mated treated females conceived versus 10 out of 11 mated control females. No differences were seen between the groups in the numbers of implantation sites per mated or per pregnant female. According to the study authors the reduced fertility in the post-coitus-only-exposed group was the result of a disturbance of the implantation process. The pre- and postcoitus-exposed animals had the opportunity to adapt to high zinc intake, thus being able to avoid the effect. However, no further studies were done to substantiate this (Pal and Pal, 1987).

In mice and rats, zinc sulphate heptahydrate in dietary concentrations up to 30,000 mg/kg feed did not produce adverse effects on either male or female sex organs after 13 weeks of exposure. This dietary level was equal to ca. 1,100 mg or 565 mg Zn^{2+}/kg bw/day for mice and rats, respectively (Maita et al., 1981; see also Section 4.1.2.7.1).

In another study, male and female rats were exposed to zinc monoglycerolate up to 1% in the diet, equal to ca. 335 mg Zn^{2+}/kg bw/day for 58 days, after which the concentration in the feed was decreased for one week to 0.5%, equal to ca. 300 mg Zn^{2+}/kg bw/day. Subsequently, the animals had to be killed at day 64 because of poor health and compromised food consumption (note also the non-linearity in the Zn^{2+}-doses). The testes of all these males showed hypoplasia of the seminiferous tubules to a varying degree and in addition the prostate and seminal vesicles showed hypoplasia. In all but one female the uterus was hypoplastic. All other rats exposed to 0.05 or 0.2% (ca. 13 or 60 mg Zn^{2+}/kg bw/day, respectively) survived to the end of the 13 weeks treatment, without showing detrimental effects on sex organs (Edwards and Buckley, 1995; see also Section 4.1.2.7.1).

Developmental toxicity

Several developmental toxicity studies with zinc sulphate and zinc oxide are available. Four studies with zinc sulphate were performed at the Food and Drugs Research Labs, Inc. (1973, 1974) and were of a design comparable to the OECD 414 guideline. These studies are mentioned in **Table 4.11** and summarised in more detail below. However, in the reports it was not specified which form of zinc sulphate was used. For this reason the NOAELs in these studies are converted to two NOAELs for Zn^{2+}, one on the assumption that the anhydrate was used and one on the assumption that the heptahydrate was used.

Table 4.11 Developmental toxicity data

Developmental toxicity	Species	Protocol	Result	mg Zn^{2+}/ kg bw	Reference
Oral	mouse	females received daily doses of 0, 0.3, 1.4, 6.5 and 30 mg $ZnSO_4$ (unspecified)/kg bw during days 6-15 of gestation.	NOAEL 30 mg/kg bw (highest dose level tested): no discernible effects were seen on nidation, or maternal or foetal survival. No difference in number of abnormalities found in foetuses	NOAEL: anhydr: 12 hepta: 6.8	Food and Drugs Research Labs., Inc. (1973)*
	rat	females received daily doses of 0, 0.4, 2.0, 9.1 and 42.5 mg $ZnSO_4$ (unspecified)/kg bw during days 6-15 of gestation.	NOAEL 42.5 mg/kg bw (highest dose level tested): no discernible effects were seen on nidation, or maternal or foetal survival. No difference in number of abnormalities found in foetuses	NOAEL: anhydr: 17 hepta: 9.6	Food and Drugs Research Labs., Inc. (1973)*
	hamster	females received daily doses of 0, 0.9, 4.1, 19, and 88 mg $ZnSO_4$ (unspecified)/kg bw during days 6-15 of gestation.	NOAEL 88 mg/kg bw (highest dose level tested): no discernible effects were seen on nidation, or maternal or foetal survival. No difference in number of abnormalities found in foetuses	NOAEL: anhydr: 35.2 hepta: 19.9	Food and Drugs Research Labs., Inc. (1973)*
	rabbit	females received daily doses of 0, 0.6, 2.8, 13 and 60 mg $ZnSO_4$ (unspecified)/kg bw during days 6-18 of gestation.	NOAEL 60 mg/kg bw: no discernible effects were seen on nidation, or maternal or foetal survival. No difference in number of abnormalities found in foetuses	NOAEL: anhydr: 24 hepta: 13.6	Food and Drugs Research Labs., Inc. (1974)*

* Valid study, with restrictions. $ZnSO_4$ form is unspecified. The NOAEL, expressed as Zn cation, has been calculation for both anhydrate- and heptahydrate forms.

Oral exposure

- Zinc sulphate

Female CD-1 mice (25-30 animals/group) received daily doses of 0.3, 1.4, 6.5 and 30 mg unspecified $ZnSO_4$/kg bw by gavage during days 6-15 of gestation. A control group was included. All animals were observed daily for appearance and behaviour with particular attention to food consumption and body weight. Body weights were recorded on day 0, 6, 11, 15 and 17 of gestation. The females were sacrificed at day 17. The urogenital tract of each animal was examined in detail. Between 21 and 23 females were pregnant at term in all groups. No clearly discernible effects on maternal survival, body weight gains, number of corpora lutea, implantations and resorptions were observed. The number of live litters, live and dead foetuses, the foetus weights and sex ratio were not affected by treatment. No difference in number or kind of abnormalities (in either soft or skeletal tissues) was found between exposed and control groups. It can be concluded that the administration of up to 30 mg/kg bw of unspecified zinc sulphate (≈12 mg or 6.8 mg Zn^{2+}/kg bw, for anhydrate and heptahydrate, respectively) had no adverse effects on adult mice and their foetuses (Food and Drug Research Labs., Inc., 1973).

Female Wistar rats (25-28 animals/group) received daily doses 0.4, 2.0, 9.1 and 42.5 mg unspecified $ZnSO_4$/kg bw by gavage during days 6-15 of gestation. A control group was included. All animals were observed daily for appearance and behaviour with particular attention to food consumption and body weight. Body weights were recorded on day 0, 6, 11, 15 and 20 of gestation. The females were sacrificed at day 20. The urogenital tract of each animal was examined in detail. At term 25 females were pregnant in all groups. No clearly discernible

effects on maternal survival, body weight gains, number of corpora lutea, implantations and resorptions were observed. The number of live litters, live and dead foetuses, the foetus weights and sex ratio were not affected by treatment. No difference in number or kind of abnormalities (in either soft or skeletal tissues) was found between exposed and control groups. It can be concluded that the administration of up to 42.5 mg/kg bw of unspecified zinc sulphate (≈17 mg or 9.6 mg Zn^{2+}/kg bw, for anhydrate and heptahydrate, respectively) had no adverse effects on adult rats and their foetuses (Food and Drug Research Labs., Inc., 1973).

Female hamsters (23-25 animals/group; outbred strain of golden hamster) received daily doses of 0.9, 4.1, 19 and 88 mg unspecified $ZnSO_4$/kg bw by gavage during days 6-10 of gestation. A control group was included. All animals were observed daily for appearance and behaviour with particular attention to food consumption and body weight. Body weights were recorded on day 0, 8, 10 and 14 of gestation. The females were sacrificed at day 14. The urogenital tract of each animal was examined in detail. Between 21 and 24 females were pregnant at term in all groups. No clearly discernible effects on maternal survival, body weight gains, number of corpora lutea, implantations and resorptions were observed. The number of live litters, live and dead foetuses, the foetus weights and sex ratio were not affected by treatment. No difference in number or kind of abnormalities (in either soft or skeletal tissues) was found between exposed and control groups. It can be concluded that the administration of up to 88 mg/kg bw of unspecified zinc sulphate (≈35.2 mg or 19.9 mg Zn^{2+}/kg bw, for anhydrate and heptahydrate, respectively) had no adverse effects on adult hamsters and their foetuses (Food and Drug Research Labs., Inc., 1973).

Female Dutch rabbits (14-19 animals/group) received daily doses of 0.6, 2.8, 13 and 60 mg unspecified $ZnSO_4$/kg bw by gavage during days 6-18 of gestation. A control group was included. All animals were observed daily for appearance and behaviour with particular attention to food consumption and body weight. Body weights were recorded on day 0, 6, 12, 18 and 29 of gestation. The urogenital tract of each animal was examined in detail. The females were sacrificed at day 29. Between 10 and 12 females were pregnant at term in all groups. No clearly discernible effects on maternal survival, body weight gains, number of corpora lutea, implantations and resorptions were observed. The number of live litters, live and dead foetuses, the foetus weights and sex ratio were not affected by treatment. No difference in number or kind of abnormalities (in either soft or skeletal tissues) was found between exposed and control groups. It can be concluded that the administration of up to 60 mg/kg bw of unspecified zinc sulphate (≈24 mg or 13.6 mg Zn^{2+}/kg bw, for anhydrate and heptahydrate, respectively) had no adverse effects on adult rabbits and their foetuses (Food and Drug Research Labs., Inc., 1974).

Female rats (13) received low protein (10%) diets containing 30 mg Zn^{2+} supplemented with 150 mg Zn^{2+}/kg feed (7.5 mg Zn^{2+}/kg bw) as 2% $ZnSO_4$ solution during days 1-18 of pregnancy. A control group (12 females) was included and received the same diet as the exposure group but without additional zinc. No further study details were given, but it was stated that two resorptions of a total number of 101 implantation sites were found in 2 (1 in each female) of the 12 control females. In 8 (at least 1 resorption each) of the 13 experimental females, 11 resorptions out of 116 implantations sites were found. This difference was reported to be statistically significant (Kumar, 1976).

Remark: The low protein diet may have affected the physiology of the animals resulting in an increased sensitivity for zinc. As this cannot be further assessed, and because virtually no study details are available, the study is not taken into account.

12 Female Charles-Foster rats received via diet 4,000 mg Zn^{2+} (as anhydrous $ZnSO_4$)/kg feed (corresponding to 200 mg Zn^{2+}/kg bw) from day 1 until day 18 post coitum and 15 animals

received the same diet from day 21-26 prior to mating until sacrifice (day 18 post coitum). Control groups consisted of 12 and 11 animals, respectively. No stillbirths or malformed fetuses were recorded and there were no significant differences in the number of resorptions or the mean placental and fetal weights between the treated females and controls irrespective of the exposure regime (Pal and Pal, 1987).

Campbell and Mills (1979) examined the reproductive performance of Cheviot sheep (6/group) which received 30, 150 and 750 mg $ZnSO_4$ (unspecified)/kg feed during pregnancy until parturition. A control group was included. High-dose sheep showed decreased food consumption, food utilisation and reduced body weight gains. Blood copper levels, plasma ceruloplasmin and amine oxidase were statistically significantly decreased and plasma zinc levels were greatly increased. The reproductive performance was severely impaired at the highest dose level: Most of the lambs were non-viable, and showed high zinc levels in the livers (this was also seen in the mid-dose) and low copper concentrations. These lambs also showed discontinuous growth of long bones, which was not observed in the lower dose groups. Copper supplementation (2.5 and 10 mg) at the high dose level prevented the development of copper deficiency, but not the other effects such as lamb viability and food consumption/utilisation.

- Zinc oxide

In rats, the administration of 0.4% of Zn^{2+} as ZnO (corresponding to 200 mg Zn^{2+}/kg bw/day) via diet for 21 days prior to mating until day 15 of gestation resulted in resorption of all foetuses. Administration of 0.4% dietary Zn^{2+} from day 0 to day 15, 16, 18 or day 20 of gestation, but not prior to mating, resulted in decreased live fetal body weights and in 4-29% fetal resorptions. When the concentration of Zn^{2+} in the feed was reduced to 0.2% (corresponding to 100 mg Zn^{2+}/kg bw /day), starting 21 days prior to mating until day 15 of gestation no resorptions or effects on fetal body weights were observed. Treatment with dietary zinc did not result in external malformations, irrespective of dose level or treatment regimen. A dose-related significant increase in liver total zinc and liver zinc concentration and a significant decrease in the liver copper concentration was found in foetuses and mothers on all zinc regiments. No other information was given with respect to the health status of the mother animals. Although some of the animals were exposed from day 21 before mating up to study termination, no data were provided on possible consequences for female fertility. The study is too limited to derive an NOAEL for developmental toxicity (Schlicker and Cox, 1968).

Groups of Sprague Dawley rats (10/group) were fed diets containing 2,000 or 5,000 mg ZnO/kg feed (calculated to be 150 or 375 mg ZnO/kg bw [≈120 or 300 mg Zn^{2+}/kg bw/day]) from day 0 of gestation to day 14 of lactation, then mothers and remaining pups were killed. The control animals received a basal diet containing 9 mg Zn^{2+}/kg feed.

Maternal weight, daily food intake, duration of gestation and the number of viable young/litter were not affected. No external malformations were seen.

Two females at 5,000 mg/kg feed had all stillborn litters containing oedematous pups. At 2,000 mg/kg feed 4 stillborn pups (not oedematous) were observed. Dry liver weights of pups (newborn and 14 days old) were decreased at 5,000 mg/kg feed. A dose-related increase in zinc content and a dose-related decrease in iron content were observed. The livers of newborns of zinc-treated dams, however, contained significantly more iron than the controls. This was not observed in the 14-day old pups. The copper levels in the liver were significantly lower only in the newborns of the 5,000 mg/kg level. After 14 days the copper concentrations were significantly lower in all treated pups (Ketcheson et al., 1969).

Bleavins et al. (1983) exposed groups of mink (11 females and 3 males/group) to basal diet (containing 20.2 mg Zn^{2+}/kg diet and 3.1 mg Zn^{2+}/kg diet) or to the diet supplemented with 1,000 mg ZnO/kg diet. No maternal effects were seen. All females on the basal diet produced offspring, 8/11 females of the Zn-supplemented diet group had young. None of the animals (males, females and kits) were sacrificed, so they were only macroscopically examined. The kits were kept on the basal and supplemented diets. The body weight of male kits on the supplemented diet was significantly lower at 12 weeks of age. 8-Week old kits on the supplemented diet showed a significant decrease of the Ht-value, the other blood parameters were comparable to the kits on basal diet. The decreased T-cell mitotic response observed in the Zn-supplemented kits was reversible when the kits were placed on basal diet. Kits (3-4 weeks old) of females fed the Zn-supplemented diet showed effects consistent with copper deficiency, such as grey fur around eyes, ears, jaws and genitals together with hair loss and dermatosis in these areas.

Inhalation exposure

No inhalation toxicity data are available.

Dermal exposure

No dermal toxicity data are available.

Other routes

- Zinc chloride

Chang (1976) reported a study in which single i.p. injections of 12.5, 20.5 or 25 mg $ZnCl_2$/kg bw (6, 9.8 or 12 mg Zn^{2+}) to CF-1 albino mice (7-15/group) on day 8, 9, 10 or 11 of gestation caused a significant dose-related increased incidence of skeletal anomalies without soft tissue anomalies. Toxic effects on mothers and foetuses were the greatest when $ZnCl_2$ was administered at 20.5 mg/kg bw on day 10 of pregnancy. When $ZnCl_2$ was given at 12.5 mg/kg bw on day 11 of gestation no effects on mothers or foetuses were observed. Because no more information was given, these results cannot be used for risk assessment.

4.1.2.10.2 Studies in humans

The majority of human studies are dealing with the association between low indices of maternal zinc status and the negative effects on pregnancy including neural tube defects in babies (Walsh et al., 1994).

Mukherjee et al. (1984) found a highly significant increase in pregnancy complications, including foetal distress and maternal infections, among women with low plasma zinc during the latter half of pregnancy. An association of low plasma zinc levels in early pregnancy and a greater likelihood of delivery of a low birth weight infant were observed by Neggers et al. (1990(*r*)). The earlier findings of Meadows et al. (1981(*r*)) reporting an association between low maternal leukocyte and muscle zinc at term and low birth weight and of Cambell-Brown et al. (1985(*r*)) reporting an association between low zinc intakes in Hindu women and low birth weight.

There are no data available indicating that an excess of zinc can impair human pregnancy outcome.

Mahomed et al. (1989) performed a study in pregnant women to examine whether zinc supplementation during pregnancy improves maternal and foetal outcome. Pregnant women were randomly assigned to receive a zinc supplementation or placebo in a double blind trial. 494 Women (246 given zinc supplementation, 248 given placebo) were followed till the end of pregnancy. The zinc supplementation was administered in capsules containing 20 mg Zn^{2+} as zinc sulphate (0.3 mg Zn^{2+}/kg bw/day) once a day during two trimesters. There were no significant differences between the two groups with respect to complications of pregnancy (weight, weight gains, maternal bleeding and hypertension), complications of labour and delivery, gestational age, Apgar scores, neonatal abnormalities and birth.

Two human studies with other zinc compounds than the ones selected showed no effects on the newborns of mothers consuming 0.3 mg Zn^{2+} (as zinc citrate)/kg bw/day (Simmer et al., 1991(*r*)) or 0.06 mg Zn^{2+} (as zinc aspartate)/kg bw/day (Kynast and Saling, 1986) during the last two trimesters of pregnancy.

4.1.2.10.3 Conclusion on toxicity for reproduction

Limited data were provided on the reproductive toxicity of zinc chloride. Data on other zinc compounds have been used, based on the assumption that after intake the biological activities of the zinc compounds are determined by the zinc cation.

For fertility no 1- or 2-generation or other applicable guideline studies are available.

When male rats were dosed with approximately about 200 mg Zn^{2+}/kg bw via the food for 30-32 days before mating, a statistically significant reduction in male reproductive performance was observed. This effect was attributed to a reduction in sperm motility. In females receiving 200 mg Zn^{2+}/kg bw, reduced conception was observed when they were dosed after mating, but not when they were dosed before and during pregnancy. It is not known whether the reduced sperm motility in males and the contradictory effects on conception in females are a direct effect of zinc on the sperm cells, embryos or uterine function, or whether they are the result of disturbances in other physiological functions. From a study by Schlicker and Cox (1968), it is known that this dose level (and even levels of 100 mg additional Zn^{2+}/kg bw/day) may result in impaired copper balance in females.

In repeated dose toxicity studies with zinc sulphate heptahydrate, no effects on the reproductive organs were seen at dose levels up to ca. 1,100 mg and 565 mg Zn^{2+}/kg bw/day for mice and rats, respectively. In a repeated dose toxicity study with zinc monoglycerolate hypoplasia of several sex organs was observed at doses of ca. 300 mg Zn^{2+}/kg bw/day, but not at 13 or 60 mg Zn^{2+}/kg bw/day. As these effects were only seen at dose levels which produced very severe general toxicity, it is impossible to conclude that these adverse effects are directly related to zinc. It should be noted that these studies are not designed to detect effects on sperm cell motility.

Developmental toxicity studies, according to a study design similar to OECD 414, with mice, rats, hamsters and rabbits were described with unspecified zinc sulphate. These studies do not permit the derivation of a proper NOAEL because neither reproductive nor developmental or maternal effects were observed, not even at the highest dose tested. When it is assumed (worst case) that the heptahydrate was administered from the study with hamsters it can be calculated that the NOAEL for both maternal effects and effects on the offspring is at least 19.9 mg Zn^{2+}/kg bw/day. In other (non-guideline) studies, higher dose levels (up to 200 Zn^{2+}/kg bw/day) have been reported to result in resorptions and retarded foetal growth, but not in external

malformations. No resorptions and growth retardation were seen at 100 mg Zn^{2+}/kg bw/day but as the study was too limited, this dose level cannot be taken as an NOAEL for developmental toxicity, either. Besides, at both 100 and 200 mg Zn^{2+}/kg bw/day changes in maternal and fetal copper status were observed. In absence of better information a NOAEL of > 19.9 mg Zn^{2+}/kg bw/day for developmental toxicity in animals is adopted.

In studies with pregnant women receiving additional 0.3 mg Zn^{2+}/kg bw/day (as zinc sulphate or citrate) during the last 6 months of pregnancy, no reproductive or developmental effects were observed. Clear evidence of zinc toxicity in human pregnancy has not been reported but this may be due to the fact that very high exposures to zinc in human pregnancy are unusual. In contrast, zinc deficiency during pregnancy can cause a variety of adverse effects on the foetus or may result in reduced fertility or delayed sexual maturation in animals as well as in humans (Walsh et al., 1994; ATSDR, 1994; WHO, 1996).

Hence, with respect to effects on reproduction, zinc deficiency is known to result in impairment of fertility and of foetal development. In humans additional zinc up to 0.3 mg Zn^{2+}/kg bw/day during pregnancy did not result in adverse effects. Available data in animals on zinc excess indicate that adverse effects on fertility and foetal development may occur at dose levels of 200 mg Zn^{2+}/kg bw/day, in conjunction with other effects such as perturbation of parental and foetal copper homeostasis. In humans a small disturbance (if any) of normal physiology, presumably indicative for copper deficiency, has been demonstrated at zinc excess of 50 and 150 mg Zn^{2+}/day (0.83 and 2.5 mg Zn^{2+}/kg bw/day, respectively), while 150 mg Zn^{2+}/day (2.5 mg Zn^{2+}/kg bw/day) resulted in clinical signs. As the margin between the dose at which in humans clinical signs are manifest and the dose at which in animals reproductive effects have been reported is so high (viz. 80), it is considered unlikely that in humans reproductive effects will occur at exposure levels at which clinical signs are not manifest. Therefore, neither fertility nor developmental toxicity are considered endpoints of concern for humans. Based on the available information there is no reason to classify metallic zinc nor any of the zinc compounds considered for reproductive toxicity.

4.1.2.11 Interaction with other chemicals

Zinc can interact with other trace elements, such as cadmium, iron, calcium and especially copper, resulting in toxicity which is usually due to depletion of these elements, leading to nutritional deficiencies. Metallothionein is involved in the interaction between zinc and other metals such as copper.

Both copper and zinc appear to bind to the same metallothionein protein, but copper has a higher affinity for it than zinc and displaces the zinc that is attached to the metallothionein (Ogiso et al., 1979*(r)*; Wapnir and Balkman, 1991*(r)*). A number of factors influence the effect of dietary zinc on copper metabolism, including the amount of copper and zinc in the diet, the zinc-to-copper ratio, age of the individual, and the duration of exposure to high zinc levels (Johnson and Flagg, 1986*(r)*).

Prasad et al. (1978*(r)*) and Porter et al. (1977*(r)*) reported that chronic, elevated intake of zinc of 100 mg or more per day induced copper deficiency in humans. Yadrick et al. (1989) and Fischer et al. (1984) observed an altered copper balance in humans at doses of 50 mg zinc/day. However, in more recent studies in which the copper status was closely monitored (Davis et al., 2000; Milne et al., 2001) the daily oral intake of 50 mg Zn^{2+} appeared to enhance rather than impair copper retention in humans.

Normally the influence of iron on zinc absorption may not be significant. Under unusual conditions, however, if large iron supplements are ingested in the absence of food, it is likely that iron could impair the zinc absorption. This is supported by a number of clinical studies (Solomons, 1988*(r)*).

Yadrick et al. (1989) studied the effect of 50 mg daily doses of supplemental zinc or 50 mg zinc together with 50 mg iron during 10 weeks in women. The results suggested that supplemental zinc at a level of 50 mg/day impaired both the iron and copper status. Simultaneous iron supplementation protected the iron status. However, in more recent studies in which the iron status was closely monitored (Davis et al., 2000; Milne et al., 2001) the daily oral intake of 50 mg Zn^{2+} did not affect indicators of iron status in humans.

Exposure to cadmium may cause changes in the distribution of zinc, with accumulation of zinc in the liver and kidney. This accumulation may result in a deficiency in other organs. Harford and Sarkar (1991*(r)*) stated that simultaneous administration of cadmium and zinc results in induction of metallothionein in an additive manner.

A high zinc intake is also associated with decreased intestinal calcium absorption, leading to decreased calcium status in the body (Yamaguchi et al., 1983*(r)*; Spencer et al., 1992*(r)*).

Conclusion on interaction with other chemicals

Zinc can interact with other trace elements, especially copper, resulting in toxicity which is usually due to depletion of these elements, leading to nutritional deficiencies. In some older studies, it has been suggested that supplemental zinc at a level of 50 mg/day impaired both the iron and copper status, but these effects were not observed in more recent interaction studies. At least part of the interaction between zinc and other metals such as copper may be related to the effect of zinc on metallothionein.

4.1.2.12 Biological function and recommended levels

Zinc is an essential element for humans and animals and it is required for the optimum function of over 200 enzymes. These enzymes include those required for normal acid, protein, and membrane metabolism, as well as cell growth and division. Zinc also plays a role in the regulation of DNA and RNA synthesis (Vallee and Auld, 1990*(r)*; South and Summers, 1990*(r)*; Berg, 1990*(r)*). Zinc is also a required element for the optimum activity of growth hormone and the normal exocrine and endocrine function of the pancreas (Lee et al., 1990*(r)*).

A zinc deficiency in the diet has been associated with loss of appetite, decreased sense of smell and taste, impaired immune function, poor wound healing and dermatitis. It can also lead to retarded growth and hypogonadism with impaired reproductive capacity. An increased incidence of congenital malformations in infants has also been associated with a zinc deficiency in the mothers (Cotran et al., 1989*(r)*; Elinder, 1986; Sandstead, 1981*(r)*).

The symptoms of zinc deficiency in children may be different from that of adults. In chronic zinc deficiency, anorexia, diarrhoea, irritability, and short stature may be predominant in children while in adults taste and smell malfunction, hypogonadism, and poor wound healing may appear as early signs. The main symptoms observed during an experimental zinc deficiency in male volunteers were loss of body weight and testicular hypofunction (Prasad, 1983).

The following daily zinc levels are recommended by NAS/NRC (1989*(r)*):

Infants (0-1 year)		5 mg/day
Children (1-10 years)		10 mg/day
Males (11-51^{+} years)		15 mg/day
Females (11-51^{+} years)		12 mg/day
Pregnant women		15 mg/day
During lactation	(first 6 months)	19 mg/day
	(next 6 months)	16 mg/day

Other authorities such as the EU (1993) or the Voedingsraad (1992) recommended somewhat lower daily levels of 9-10 mg/day and 7-9 mg/day for males and females, respectively.

Conclusion on biological function and recommended levels

Zinc is an essential element required for the function of a large number of enzymes. It plays a role in DNA and RNA synthesis and many other processes in the body. A zinc deficiency in the diet can lead to notable health effects. Recommended daily zinc levels range from 5 mg/day for infants to 19 mg/day for women during lactation.

4.1.3 Risk characterisation

4.1.3.1 General aspects

The human population may be exposed to zinc chloride at the workplace, from uses of consumer products and indirectly via the environment (see Sections 4.1.1.2, 4.1.1.3, 4.1.1.4).

Large parts of the hazard section are identical in the risk assessment reports on the six zinc compounds now under review under EU Regulation 793/93. This is because of the basic assumption that the zinc cation (as measure for dissolved zinc species) is the determining factor for systemic toxicity.

It is realised that for zinc (and other metal) compounds it would be important to define the actual or bioavailable concentration which is important for toxicity, both in laboratory animals and in humans. Due to several physico-chemical processes, zinc will exist in different chemical forms, some of which are more bioavailable than others. It is thus realised that the bioavailability is affected by various physico-chemical parameters (ionic behaviour, solubility, pH, alkalinity etc.). Although there is some information on the solubility of the six zinc compounds, adequate information is lacking how to quantitatively determine or estimate the bioavailable fraction of all the different zinc compounds in either laboratory animals or humans. Therefore, it is assumed that all zinc compounds (including metallic zinc) are changed (at least in part) to the ionic species, and all toxicity data (independent of the tested compound) were used and expressed as the zinc cation.

With respect to local effects, it is not always possible to use data from all zinc compounds. Hence, for local effects only data from the specific zinc compound were used, or, where there were derogations, data from zinc compounds with more or less the same solubility characteristics.

A problem might arise for the route-to-route extrapolation for inhalation and dermal exposure, since the differences in physico-chemical properties of the zinc compounds can change the toxicokinetics (absorption) and subsequently the toxic effects. Although it is possible to predict the systemic effects after inhalation or dermal exposure from oral toxicity data of the zinc compound itself or other zinc compounds, this is only justifiable after careful consideration of all available data to establish adequate extrapolation factors.

Furthermore it is assumed that the influence of the background intake levels of zinc cations in animal studies will be the same for humans.

Several data were provided on the toxicokinetics of zinc chloride. Data on other zinc compounds have also been used, as the basic assumption is made that after intake all zinc compounds (including metallic zinc) are changed (at least in part) to the ionic species and that it is this zinc cation that is the determining factor for the biological activities of the zinc compounds.

Within certain limits, the total body zinc as well as the physiologically required levels of zinc in the various tissues can be maintained, both at low and high dietary zinc intake. Regulation of gastrointestinal absorption and gastrointestinal secretion probably contributes the most to zinc homeostasis. In spite of this a regular exogenous supply of zinc is necessary to sustain the physiological requirements because of the limited exchange of zinc between tissues.

The Zn^{2+} absorption process in the intestines includes both passive diffusion and a carrier-mediated process. The absorption can be influenced by several factors such as ligands in the diet and the zinc status.

Persons with adequate nutritional levels absorb 20-30% and animals 40-50%. However, persons that are Zn-deficient absorb more, while persons with excessive Zn intake absorb less. For risk assessment, for the more soluble zinc compounds (chloride, sulphate) the lower bound of the absorption range at adequate nutritional levels is taken (i.e. 20%). For zinc oxide it has been shown that bioavailability is about 60% of that for soluble zinc salts, corresponding to 12-18%. For zinc metal, zinc phosphate and zinc distearate no bioavailability data were present. As these forms have limited solubility in diluted acids (stomach) comparable to zinc oxide, for the less soluble zinc compounds (oxide, phosphate, distearate, metal) an oral absorption value of 12% will be taken for risk assessment. In situations of exposure excess (e.g. in case of high dermal or inhalation exposure at the workplace) the oral uptake of zinc compounds will probably be less than the values taken for risk assessment (20% and 12%). However, as this reduction in uptake is not quantifiable, also for excess exposure situations the same oral absorption values will be applied. Some justification for this approach can be found in the observation that for intake levels differing by a factor of 10, uptake levels vary maximally by a factor of two.

Quantitative data on the absorption of zinc following inhalation exposure (especially relevant in occupational settings) are not available. Some animal data suggest that pulmonary absorption is possible. In animal studies on zinc oxide retention in the lungs half-life values of 14 and 6.3 hours were reported for dissolution. As the absorption of inhaled zinc depends on the particle size and the deposition of these particles, data were provided on the particle size distribution of zinc aerosol in three different industry sectors. When analysing the particle size distribution data with a multiple path particle deposition (MPPDep) model, it appeared that for zinc aerosols the largest part of the deposition takes place in the head region and much less in the tracheobronchial and pulmonary region. Although most of the material deposited in the head and tracheobronchial region is rapidly translocated to the gastrointestinal tract, a part will also be absorbed locally. Based on data for local absorption of radionuclides in the different airway regions, it is assumed that local absorption for the soluble zinc compounds will amount to 20, 50 and 100% of the material deposited in head, tracheobronchial and pulmonary region, respectively. For the less soluble/insoluble zinc compounds negligible absorption is assumed for head and tracheobronchial region and 100% absorption for the pulmonary region. The remaining part of the material deposited in the different airway regions will be cleared to the gastrointestinal tract where it will follow oral uptake kinetics, hence the oral absorption figures can be applied. Applying the above mentioned assumptions to the deposition fractions as determined by the MPPDep model, inhalation absorption for the soluble zinc compounds (zinc chloride and zinc sulphate) is at maximum 40%, while for the less soluble/insoluble zinc compounds (zinc metal, zinc oxide, zinc phosphate and zinc distearate) inhalation absorption is at maximum 20%. These figures will be taken forward to the risk characterisation as a reasonable worst case, because these figures are thought to cover existing differences between the different zinc industry sectors with respect to type of exercise activities (and thus breathing rate) and particle size distribution.

Adequate quantitative data on the absorption of zinc following dermal exposure (relevant in both occupational and consumer settings) are not available. The human data presented are not considered valid, mainly since either wounded skin was investigated, or suction blisters were raised, impairing the intactness of the skin. Dermal absorption through the intact skin seems to be small (< 2%), based on the results of the *in vivo* animals studies as well as the *in vitro* studies, but unfortunately shortcomings were noted in all *in vivo* studies and none of these studies can be used quantitatively. As for the *in vitro* studies, it is clear that the % in receptor medium generally gives an underestimation of the % systemically available in *in vivo* studies. Therefore, the

amount detected in the skin should be included as being absorbed by default. This 'potentially absorbed dose' more closely resembles the dose becoming systemically available *in vivo*.

Zinc bound to or in the skin may become systemically available at a later stage. This can be concluded from results in TPN patients, in which an expected decrease in serum zinc levels with time was counteracted by dermal absorption of zinc to result in steady serum zinc levels. Unfortunately, only 3 of the 6 patients completed the 10-day study period. There are no adequate human data available to evaluate the release of zinc from normal skin following single or repeated dermal exposure, as either blood was sampled for a too short period of time (3 hours; Derry et al., 1983) or the skin was damaged (Agren, 1990, 1991; Hallmans, 1977). Therefore, it can be concluded that following single or repeated dermal exposure zinc can be taken up by the skin, whereas the relevance of this skin depot cannot be judged based on the available data. For example, it is not studied how a large artificial zinc depot in the skin will affect the uptake or homeostasis of other essential ions (e.g. Cu). However, the total database available indicates that skin-bound zinc may not become systemically available in a way that it results in high peak levels of zinc in serum, but rather in a more gradual way. Given the efficient homeostatic mechanisms of mammals to maintain the total body zinc and the physiologically required levels of zinc in the various tissues constant, the anticipated slow release of zinc from the skin is not expected to disturb the homeostatic zinc balance of the body. By expert judgement, based on the aforementioned considerations, the default for dermal absorption of solutions or suspensions of zinc or zinc compounds is therefore chosen to be 2%. Based on the physical appearance, for dust exposure to zinc or zinc compounds a 10-fold lower default value of 0.2% is chosen in the risk assessment.

Zinc is distributed to all tissues and tissue fluids and it is a cofactor in over 200 enzyme systems.

Zinc is primarily excreted via feces, but can also be excreted via urine, saliva, hair loss, sweat and mothermilk.

Zinc chloride is harmful after acute oral exposure. Zinc chloride can be toxic or even very toxic after acute inhalatory exposure, and given the fact that effects are seen on lung tissue after intratracheal dosing as well, particle size may not be that relevant for inhalatory toxicity. In addition, inhalation exposure to zinc chloride can cause irritation of the respiratory system.

Zinc chloride causes burns and is corrosive. Data on skin sensitisation are not available for zinc chloride. However, based on the accepted derogation and the fact that zinc sulphate is not a skin sensitiser, it is consequently concluded that zinc chloride is not likely to be skin sensitising.

Limited data were provided on the repeated dose toxicity of zinc chloride. Data on other zinc compounds have been used, based on the assumption that after intake the biological activities of the zinc compounds are determined by the zinc cation.

No repeated dose toxicity studies after dermal exposure are available in animals.

After inhalation exposure mainly studies of short duration (3-6 days) are available. In a 3-day inhalation study with guinea pigs a concentration of 2.3 mg ultrafine ZnO/m^3 (3 hours/day) was a marginal LOAEL, showing changes in neutrophils and activities of lactate dehydrogenase and alkaline phosphatase in the pulmonary fluid. At higher concentrations increased protein concentration, neutrophils, and enzyme activities in lung lavage fluids were seen, together with significant centriacinar inflammation of the pulmonary tissue. A dose of 2.7 mg ultrafine ZnO/m^3 (3 hours/day for 5 days) did not alter the lung function parameters in guinea pigs but at 7 mg ultrafine ZnO/m^3 (3 hours/day for 5 days) or at 5 mg ultrafine ZnO/m^3 (3 hours/day for

6 days) a gradual decrease in total lung capacity, vital capacity and reduction of the carbon monoxide diffusing capacity were seen in combination with inflammatory changes and edema. The relevance of the findings in studies with ultra-fine zinc oxide fumes is unclear with respect to commercial grade zinc oxide, as the latter is of much larger particle size and can have different toxicological characteristics.

In two oral 13-week studies with zinc sulphate (one with rats and one with mice) and an oral 13-week study with zinc monoglycerolate in rats, the lowest oral NOAEL was found in the study with zinc monoglycerolate. This overall NOAEL is 31.52 mg zinc monoglycerolate/kg bw (≈ 13.26 mg Zn^{2+}/kg bw). At higher doses the most important effects the rats developed were hypocupremia, and significant changes in the pancreas (focal acinar degeneration and necrosis) and the spleen (decreased number of pigmented macrophages). It should be noted that in the studies with zinc sulphate mice and rats could be maintained up to 13 weeks on a diet containing 30,000 mg $ZnSO_4.7\ H_2O$/kg feed (equivalent to 6,794 mg Zn^{2+}/kg feed), while in the 13-week study with zinc monoglycerolate with rats 1.0% zinc monoglycerolate in the diet (equivalent to 4,420 mg Zn^{2+}/kg feed) was so detrimental that animals had to be killed on humane grounds after 9 weeks.

Upon supplementing men and women with 150 mg Zn^{2+}/day (as zinc sulphate capsules), women appeared to be more sensitive than men to the effects of high zinc intake: clinical signs such as headache, nausea and gastric discomfort were more frequent among women, and women but not men had decreased activities of serum ceruloplasmin and erythrocyte superoxide dismutase (ESOD). In some earlier oral studies in which humans were supplemented with moderately high amounts of zinc (50 mg Zn^{2+}/day), a reduction in ESOD activity was also observed and again women appeared to be more sensitive to this effect. Hence, a reduction in ESOD was thought to be a sensitive indicator of copper status. However, in more recent and more sophisticated studies using the same dose level, ESOD was only marginally reduced (without a correlation with changes in copper balance), while findings on more specific copper deprivation signs (decreased serum ceruloplasmin and platelet cytochrome c oxidase) indicated that a sub-optimal intake of zinc was more effective than a moderately high intake of zinc in inducing changes associated with a decreased copper status in postmenopausal women. Given this, and degree of the observed ESOD reduction in comparison to the natural variability in its activity, the zinc-induced decrease in ESOD activity is considered to have marginal biological significance, if any, also because it may not have been caused by an interference with copper metabolism.

Overall, it is concluded from studies in which humans were supplemented with zinc (as zinc gluconate), that women are more sensitive to the effects of high zinc intake and that a dose of 50 mg Zn^{2+}/day is a NOAEL. At the LOAEL of 150 mg Zn^{2+}/day, clinical signs and indications for disturbance of copper homeostasis have been observed. The human oral NOAEL of 50 mg Zn^{2+}/day (0.83 mg/kg bw/day) will be taken across to the risk characterisation.

Several data were provided on the genotoxicity of zinc chloride. Data on other zinc compounds have also been used, based on the assumption that after intake the biological activities of the zinc compounds are determined by the zinc cation. The available data indicate that the genotoxicity results vary widely. Conflicting results have been found, even in the same test systems. Overall, the results of the *in vitro* tests indicate that zinc has genotoxic potential *in vitro* based on positive results in mammalian test systems for gene mutations and chromosomal aberrations and on the positive *in vitro* UDS test. The positive result for chromosomal aberrations *in vitro* is considered overruled by negative *in vivo* tests for this endpoint. The positive sperm head abnormality test is considered sufficiently counter-balanced by two negative SLRL tests as well as two negative dominant lethal tests.

Based on the available data there is insufficient ground to classify zinc as genotoxic. It should be noted that the potential to induce gene mutations was not adequately tested *in vivo*. However, there is no clear evidence from the available data that zinc is genotoxic *in vivo* and without a clear indication for carcinogenicity (see below) guidance for further testing with respect to target tissue is not available.

The limited data available indicate that zinc deficiency or supplementation may influence carcinogenesis, since promoting and inhibiting actions have been reported. However, there is no clear experimental or epidemiological evidence for a direct carcinogenic action of zinc or its compounds.

Limited data were provided on the reproductive toxicity of zinc chloride. Data on other zinc compounds have been used, based on the assumption that after intake the biological activities of the zinc compounds are determined by the zinc cation.

For fertility no 1- or 2-generation or other applicable guideline studies are available.

When male rats were dosed with approximately about 200 mg Zn^{2+}/kg bw via the food for 30-32 days before mating, a statistically significant reduction in male reproductive performance was observed. This effect was attributed to a reduction in sperm motility. In females receiving 200 mg Zn^{2+}/kg bw, reduced conception was observed when they were dosed after mating, but not when they were dosed before and during pregnancy. It is not known whether the reduced sperm motility in males and the contradictory effects on conception in females are a direct effect of zinc on the sperm cells, embryos or uterine function, or whether they are the result of disturbances in other physiological functions. From a study by Schlicker and Cox (1968), it is known that this dose level (and even levels of 100 mg additional Zn^{2+}/kg bw/day) may result in impaired copper balance in females.

In repeated dose toxicity studies with zinc sulphate heptahydrate, no effects on the reproductive organs were seen at dose levels up to ca. 1,100 mg and 565 mg Zn^{2+}/kg bw/day for mice and rats, respectively. In a repeated dose toxicity study with zinc monoglycerolate hypoplasia of several sex organs was observed at doses of ca. 300 mg Zn^{2+}/kg bw/day, but not at 13 or 60 mg Zn^{2+}/kg bw/day. As these effects were only seen at dose levels which produced very severe general toxicity, it is impossible to conclude that these adverse effects are directly related to zinc. It should be noted that these studies are not designed to detect effects on sperm cell motility.

Developmental toxicity studies, according to a study design similar to OECD 414, with mice, rats, hamsters and rabbits were described with unspecified zinc sulphate. These studies do not permit the derivation of a proper NOAEL because neither reproductive nor developmental or maternal effects were observed, not even at the highest dose tested. When it is assumed (worst case) that the heptahydrate was administered from the study with hamsters it can be calculated that the NOAEL for both maternal effects and effects on the offspring is at least 19.9 mg Zn^{2+}/kg bw/day. In other (non-guideline) studies, higher dose levels (up to 200 Zn^{2+}/kg bw/day) have been reported to result in resorptions and retarded foetal growth, but not in external malformations. No resorptions and growth retardation were seen at 100 mg Zn^{2+}/kg bw/day but as the study was too limited, this dose level cannot be taken as an NOAEL for developmental toxicity, either. Besides, at both 100 and 200 mg Zn^{2+}/kg bw/day changes in maternal and fetal copper status were observed. In absence of better information a NOAEL of > 19.9 mg Zn^{2+}/kg bw/day for developmental toxicity in animals is adopted.

In studies with pregnant women receiving additional 0.3 mg Zn^{2+}/kg bw/day (as zinc sulphate or citrate) during the last 6 months of pregnancy, no reproductive or developmental effects were

observed. Clear evidence of zinc toxicity in human pregnancy has not been reported but this may be due to the fact that very high exposures to zinc in human pregnancy are unusual. In contrast, zinc deficiency during pregnancy can cause a variety of adverse effects on the foetus or may result in reduced fertility or delayed sexual maturation in animals as well as in humans (Walsh et al., 1994; ATSDR, 1994; WHO, 1996).

Hence, with respect to effects on reproduction, zinc deficiency is known to result in impairment of fertility and of foetal development. In humans additional zinc up to 0.3 mg Zn^{2+}/kg bw/day during pregnancy did not result in adverse effects. Available data in animals on zinc excess indicate that adverse effects on fertility and foetal development may occur at dose levels of 200 mg Zn^{2+}/kg bw/day, in conjunction with other effects such as perturbation of parental and foetal copper homeostasis. In humans a small disturbance (if any) of normal physiology, presumably indicative for copper deficiency, has been demonstrated at zinc excess of 50 and 150 mg Zn^{2+}/day (0.83 and 2.5 mg Zn^{2+}/kg bw/day, respectively), while 150 mg Zn^{2+}/day (2.5 mg Zn^{2+}/kg bw/day) resulted in clinical signs. As the margin between the dose at which in humans clinical signs are manifest and the dose at which in animals reproductive effects have been reported is so high (viz. 80), it is considered unlikely that in humans reproductive effects will occur at exposure levels at which clinical signs are not manifest. Therefore, neither fertility nor developmental toxicity are considered endpoints of concern for humans.

Zinc can interact with other trace elements, especially copper, resulting in toxicity which is usually due to depletion of these elements, leading to nutritional deficiencies. In some older studies, it has been suggested that supplemental zinc at a level of 50 mg/day impaired both the iron and copper status, but these effects were not observed in more recent interaction studies. At least part of the interaction between zinc and other metals such as copper may be related to the effect of zinc on metallothionein.

Zinc is an essential element required for the function of a large number of enzymes. It plays a role in DNA and RNA synthesis and many other processes in the body. A zinc deficiency in the diet can lead to notable health effects. Recommended daily zinc levels range from 5 mg/day for infants to 19 mg/day for women during lactation.

For the risk characterisation, an overall oral NOAEL of 50 mg Zn^{2+}/day (0.83 mg/kg bw/day) is set on the human volunteer study by Grand Forks (Davis et al., 2000; Milne et al., 2001). Given that this study was with women (the most sensitive population in zinc supplementation studies), and that in women clinical signs begin to appear only at a dose three times this NOAEL, a minimal MOS of 1 is considered sufficient when comparing the human NOAEL with the exposure levels for workers/consumers/general population.

Note: In the absence of useful dermal and inhalation toxicity studies, in the risk characterisation no distinction is made for systemic exposure to zinc via oral, dermal or inhalation exposure. For inhalation exposure this seems reasonable, given that the majority of the inhaled zinc is cleared via the gastro-intestinal tract. It is not entirely clear whether this route-to-route extrapolation, using the oral NOAEL as starting point, is also justified for dermal exposure. This is because it is not certain whether the effects of zinc on copper homeostasis at higher doses are only the result of a local interference of zinc with the regulation of copper absorption or that also systemic factors are involved. For a worst-case approach it will be assumed that it is possible to evaluate the systemic effects after dermal exposure to zinc based on the oral NOAEL.

Previously, other organisations have evaluated the toxicity data of zinc, also taking into account that zinc is an essential element. In these evaluations the information generated in the Grand

Forks study has not been considered, because this study is of more recent date. For sake of completeness the opinions of these organisations are given below.

In 1982, the WHO set a provisional maximum tolerable daily intake for zinc at 0.3-1.0 mg/kg bw (basis not quite clear). Later on, several scientific committees have based their recommendation for a maximum daily intake (EU, 1993; Gezondheidsraad, 1998) or oral reference dose (US EPA, 1992) on the study in humans by Yadrick et al. (1989). This study was also taken into account by WHO in 1996. Because the dose of 50 mg Zn^{2+} was additional to the amount of zinc that was already in the normal diet (approximately 10 mg Zn^{2+}/day), the US EPA (1992) recalculated the LOAEL to be approximately 60 mg/day (1 mg/kg bw/day). By using an uncertainty factor of 3 (based on a minimal LOAEL from a moderate-duration study of the most sensitive humans and consideration of a substance that is an essential dietary nutrient) they set an oral reference dose of 0.3 mg/kg bw/day for zinc and zinc compounds. The EU (1993) stated that as "short-term intakes of about 50 mg zinc daily interfered with the metabolism of both iron and copper (Yadrick et al., 1989), it would be unwise to exceed a daily zinc intake of 30 mg in adults". The Dutch Health Council (Gezondheidsraad, 1998) followed this recommendation. The WHO (1996) stated that "interactions with other nutrients influencing their absorption and utilization have been detected biochemically at total zinc intakes as low as 60 mg/day when zinc was given in the form of a supplement to a diet that, it is reasonable to assume, already provided 10 mg of zinc/day". In order "to ensure that very few individuals in a population have an intake of zinc of 60 mg or higher, the Expert Consultation recommended that the adult population mean intake should not exceed 45 mg if a 20% variation in intake is assumed" (WHO, 1996).

4.1.3.2 Workers

Assuming that oral exposure is prevented by personal hygienic measures, the risk characterisation for workers is limited to the dermal and inhalation routes of exposure. During production, workers are inhalatory and dermally (dust) exposed to $ZnCl_2$. During galvanising workers are exposed by inhalation to zinc chloride but also to zinc oxide aerosols. During galvanising also dermal exposure to zinc oxide (dust) and zinc chloride (dust) may occur. During the maintenance of flux baths respiratory exposure is possible to zinc chloride (dust). Dermal exposure during maintenance of flux baths is assumed to be negligible because the temperature in flux baths is too extreme for dermal contact.

For risk assessment it is distinguished whether it concerns exposure to zinc oxide or zinc chloride, and the physical form is also taken into account. For the toxicity data reference is made to the risk assessment reports of zinc oxide and zinc sulphate.

4.1.3.2.1 Acute toxicity

Exposure to zinc chloride

Zinc chloride should be classified as very toxic after inhalation exposure. For occupational risk assessment the short-term inhalation exposure levels (6.4 mg $ZnCl_2/m^3$ (1 hour) during production of $ZnCl_2$ powders and flux solutions, 1.1 mg $ZnCl_2/m^3$ (15 min) to aerosols for "galvanising", and 0.25 mg/m^3 (0.5 hour) to dust for "maintenance of flux baths", see **Table 4.4**) are compared with the LC50 value in rats (≤ 1,975 mg/m^3, 10 minutes of exposure). The MOS-values are evaluated taking into account inter- and intraspecies differences, dose-response curve and severity of the effects. There are no reasons to deviate from the default values for the

first two aspects (factor 3 for both, see Hakkert et al., 1996). Assessment factors for the two last factors cannot be derived, but it is noted that the MOS value is calculated for a severe effect (lethality). Given the calculated MOS-values, $\leq$ 309 $\leq$ 7,900, it is expected that there is no risk for lethality after inhalation exposure. Besides lethality also respiratory distress and microscopic findings in the lungs were observed at 1,975 mg/m^3. It is noted that in the acute inhalation study, very small particle size droplets were used, which might not reflect exposure to inhalable dust under normal conditions. The calculated MOS values are considered to be large enough, and it is concluded that there is no risk for acute toxicity after inhalation exposure: **conclusion (ii)**.

Acute toxicity studies with zinc chloride performed by dermal administration are not available. Zinc chloride is very toxic after inhalation and harmful after oral administration. The most pronounced effect after single dermal exposure at the workplace would be irritation, but either direct systemic effects or indirect systemic effects, as consequence of skin reactions, cannot be excluded. However, in view of the anticipated limited bioavailability following dermal exposure **conclusion (ii)** is reached for the dermal route in the scenario "production of zinc chloride" (dermal exposure 420 mg zinc chloride/day) and the subscenario "galvanising"(dermal exposure 290 mg zinc chloride/day).

There is no risk for dermal exposure in the subscenario "maintenance of flux baths" either, because dermal exposure is estimated to be negligible: **conclusion (ii)**.

Exposure to zinc oxide (subscenario "galvanising")

For occupational risk assessment the short-term inhalation exposure level (0.7 mg ZnO/m^3, 15 min) (see **Table 4.4**) is compared with LC50 values (2,500 mg/m^3 in mice, > 5,700 mg/m^3 in rats, see Risk assessment report on of zinc oxide). The MOS values (3,571 > 8,143) are evaluated taking into account inter- and intraspecies differences, dose-response curve and severity of the effects. There are no reasons to deviate from the default values for the first two aspects (factor 3 for both, see Hakkert et al., 1996). Assessment factors for the two last factors cannot be derived, but it is noted that the MOS values are calculated for a severe effect (lethality). Given the calculated MOS-values, it is expected that there is no risk for lethality after inhalation exposure to zinc oxide: **conclusion (ii)**.

However, metal fume fever symptoms were observed in humans exposed for 2 hours to 5 mg/m^3 (see Risk assessment report on zinc oxide). Metal fume fever is only related to very fine particles. During galvanising exposure to very fine particles is estimated to be 0.1 mg ZnO/m^3. Comparison of the effect level (5 mg/m^3) with the exposure level of fine particles (0.1 mg/m^3) results in a MOS of 50 for metal fume fever. Because the effect level was observed in humans, application of additional assessment factors is not considered necessary. Therefore it is concluded that the MOS of 50 is large enough to conclude that there is no concern for metal fume fever due to inhalation exposure to zinc oxide in this scenario: **conclusion (ii)**.

In the subscenario "galvanising" dermal exposure to zinc oxide may occur (174 mg ZnO/day, assuming total zinc is 100% zinc oxide). Acute toxicity studies performed by dermal administration are not available. As the oral toxicity study with zinc oxide has an LD50 > 5,000 mg/kg bw and dermal absorption for zinc oxide is expected to be low, there is no concern with respect to acute toxicity (lethality) after dermal exposure: **conclusion (ii)**.

Furthermore, the results from the oral toxicity study do not point to other systemic effects and thereby to reasons for concern after single dermal exposure.

4.1.3.2.2 Irritation and corrosivity

Skin

The corrosive properties of $ZnCl_2$ at 1 mg/cm^2 and the dermal occupational exposure level 0.21 or 0.14 mg/cm^2 (production or galvanising, respectively, 420 or 290 mg zinc chloride/day; assuming an exposed skin area of 2,030 cm^2), results in MOSs of 5 and 7, respectively, based on an effect level. The toxicity data available does not allow an estimation of the no-effect concentration. Therefore, it is concluded that zinc chloride is of concern for workers with regard to acute skin irritation and corrosivity in the production scenario and the subscenario "galvanising". However, if the required protection (based on R34 classification) is strictly adhered to, **conclusion (ii)** is justifiable.

Because dermal exposure to zinc chloride is negligible in the subscenario "maintenance of flux bath": **conclusion (ii)** is drawn in this case as well.

Eye

Exposure to the eyes is possible via aerosols (zinc chloride, zinc oxide) or dusts (zinc chloride). Data on eye irritating effects of zinc chloride are not available. Given the skin irritating and corrosive properties of $ZnCl_2$, it is concluded that risk reduction measures are indicated to avoid eye irritation. However, if the required protection is strictly adhered to, **conclusion (ii)** is justifiable. Based on the results of the eye irritation studies with zinc oxide (see Risk assessment report on zinc oxide) it is concluded that eye exposure to this substance will not contribute to the risk of adverse eye effects.

Respiratory tract

Exposure to zinc chloride

In laboratory animals, inhalation as well as intratracheal exposure to zinc chloride led to local effects in the respiratory tract. Local effects in the respiratory tract were also reported by humans accidentally exposed to zinc chloride fumes. Given the fact that effects are seen on respiratory tissues after intratracheal dosing as well, particle size may not be that relevant for the occurrence of local effects. The particle size distribution will however determine at what level in the respiratory tract effects will occur.

In humans, a 30-min inhalation exposure to zinc chloride fumes at 0.4 mg/m^3 appeared to be without effects, whereas at 4.8 mg/m^3 mild transient irritation of the respiratory tract was seen. The MOS between this effect level and the estimated short-term exposure levels (6.4 mg $ZnCl_2$/m^3 1 hour during production; 1.1 mg $ZnCl_2$/m^3, 15 min in the subscenario "galvanising"; 0.25 mg/m^3, 0.5 hour in the subscenario "maintenance of flux baths") are 0.8, 4.4, and 19, respectively, based on an effect level. Although it is recognised that exposure in the concerning exposure scenarios is to much larger particles, it cannot be excluded in the scenario production of zinc chloride that local effects may occur in the upper airways, including nose. Therefore, **conclusion (iii)** is reached for this scenario.

The MOS of 4.4 represents a borderline case, but is considered sufficient to cover the uncertainties about the true no-effect level (extrapolation from a LOAEL to a NAEL) and remaining intraspecies differences (LOAEL derived from worker population). Therefore, it is

concluded that there is no concern for the subscenario "maintenance of flux baths" and the subscenario "galvanising'": **conclusion (ii)**.

Exposure to zinc oxide aerosol (subscenario "galvanising")

Based on a well-performed acute inhalation study with commercial grade zinc oxide (see risk assessment report on zinc oxide) it can be concluded that zinc oxide is of no concern with respect to respiratory irritation: **conclusion (ii)**.

4.1.3.2.3 Sensitisation

No dermal sensitisation studies with zinc chloride are available. However, a derogation was accepted that given the corrosive properties of zinc chloride and the fact that for the Cl-ion no sensitisation can be expected, data from another soluble zinc compound (i.e. zinc sulphate) could be used. From studies with mice and guinea pigs it was concluded that zinc sulphate has no skin sensitising properties (see Risk assessment report on zinc sulphate). Consequently, it is concluded that zinc chloride is not skin sensitising and therefore does not need to be classified/labelled: **conclusion (ii)**.

4.1.3.2.4 Repeated dose toxicity

Because there are no dermal and respiratory repeated dose toxicity studies on zinc chloride or zinc oxide, risk characterisation for local skin and respiratory effects after repeated exposure to these substances in the occupational exposure scenarios under consideration cannot be described and it is unknown whether local or systemic effects of zinc chloride and zinc oxide are critical. Risk characterisation is limited to the systemic effects of the Zn^{2+}-ion. For systemic toxicity the data from soluble zinc compounds can be used for determining specific systemic toxicity of zinc with the ion release rate of zinc becoming the factor that determines the dose. Because zinc oxide has a low solubility, this will result in a worst-case estimate for these substances.

The NOAEL of 50 mg Zn^{2+}/day derived from a 10-week oral study with human volunteers is used as a starting point for the risk characterisation for repeated dose toxicity. This NOAEL of 50 mg Zn^{2+}/day results in an internal NOAEL of 10 mg Zn^{2+}/day by correction for oral absorption (20%; worst case, because of the homeostasis the relative absorption will be smaller by excess of Zn^{2+}-intake (see Section 4.1.2.1.6)). The occupational health risk due to the $ZnCl_2$ exposure is determined by comparing the internal NOAEL of 10 mg Zn^{2+}/day with the internal occupational exposure.

The dermal levels of zinc total and the respiratory exposure levels of zinc chloride and zinc oxide for the occupational scenarios (see Section 4.1.1.2 and **Table 4.4**) are estimated. These levels are used as a starting point in determining the internal exposure level due to occupational exposure, by correction for dermal and inhalation absorption, respectively. Inhalation exposure to zinc chloride and zinc oxide in the subscenario "galvanising" may occur simultaneously. Therefore, the internal exposure due to inhalation is determined by the sum of both levels. For zinc chloride, 40% respiratory absorption is assumed (see Section 4.1.2.2). For zinc oxide, 20% respiratory absorption is assumed. For dermal absorption 0.2% is taken into account, because Zn^{2+}-ions (dust) are only slightly absorbed through the skin (see Section 4.1.2.1.6).

The MOSs between the internal NOAEL and the internal occupational exposure estimates are mentioned in **Table 4.12**. The MOSs are evaluated by comparison with the minimal MOS. Since

the NOAEL that is used as a starting point is derived from a study with human volunteers, a minimal MOS of 1 is considered appropriate (see Section 4.1.3.1). There is concern when the calculated MOS is significantly lower than the minimal MOS.

Table 4.12 Occupational risk assessment of zinc chloride and zinc oxide for repeated dose toxicity after dermal and inhalation exposure (systemic effects)

	Risk characterisation for dermal and inhalation exposure			
Substance	**Estimated external dermal exposure in mg Zn2+/day (between brackets internal exposure in mg Zn2+/day) a)**	**MOS b)**	**Estimated external inhalation exposure in mg Zn2+/m3 (between brackets internal exposure in mg Zn2+/day) c)**	**MOS b)**
Production of powders and flux solutions #				
Zinc chloride	200 (0.4)	25	0.2 (0.8)	13
Galvanising #				
Zinc chloride and zinc oxide (simultaneous exposure)	140 (0.3)	33	0.2 + 0.2 (0.8 + 0.4 = 1.2)	8.3

\# The risk assessment for repeated exposure is only based on full shift exposure levels, since these also include short-term activities such as cleaning and maintenance. It is noted that possible higher risks resulting from daily performance of these activities associated with higher short-term exposures, are not accounted for. Exposure during maintenance of flux baths is not assumed to be of relevance for risk assessment after repeated exposure

a) Estimated internal dermal exposure to Zn^{2+} used for calculating the risk, assuming a dermal absorption of 0.2% (dust);

b) MOS values based on comparison of the internal NOAEL of 10 mg Zn^{2+}/day with the internal exposure.;

c) Estimated internal inhalation exposure to Zn^{2+} used for calculating the risk, assuming a respiratory absorption of 40% for zinc chloride and 20% for zinc oxide, and an inhalation volume of 10 m^3. Because in the scenario 'galvanising' exposure to zinc chloride and zinc oxide may occur simultaneously, the internal levels are added.

Given the calculated MOS values for dermal and inhalation exposure as mentioned in **Table 4.12**, it is concluded that, based upon the present information, health risks due to occupational dermal and inhalation exposure are not likely to occur taking into account the worst-case estimates made: **conclusion (ii)**.

The risk characterisation for systemic effects is made with several assumptions:

- the internal values are calculated with worst-case assumptions for percentages absorption,
- it is assumed that other factors influencing route-specificity are not of importance. In case of Zn^{2+}, metabolism does not play a role, which favours this assumption,
- the human study was not performed with $ZnCl_2$, so it is assumed that the effects are due to Zn^{2+},
- the background intake of zinc in the experimental situation (human) and in workers are comparable,
- the background intake via food is considered to be comparable in the different EU countries,
- physiological role of Zn^{2+} is comparable between species.

The NOAEL was derived from a human volunteer study, in which a restricted amount of parameters was used. As the toxicity study with rats showed more specific adverse effects (pancreas), the results from this toxicity study are used for comparison. Starting with the NOAEL of 31.52 mg zinc monoglycerolate/kg bw/day (corresponding with 13.3 mg Zn^{2+}/kg bw/day and 27.6 mg $ZnCl_2$/kg bw/day) from the 13-week study with rats, results in an internal NOAEL of 5.3 mg Zn^{2+}/kg bw/d or 372 mg Zn^{2+}/day for a 70 kg worker (see Appendix A). The

calculated MOSs are 930-1,240 and 310-465 for internal dermal and inhalation exposure, respectively. Comparing these values with the minimal MOS of 360 (see Appendix A), and noting that this approach will be far too conservative for the essential nutrient zinc, it is concluded that risk characterisation based on the human study is adequate to protect also against adverse effects as observed in animal studies.

Combined exposure

The assessment of the risk after combined exposure (i.e., the risk due to the internal exposure resulting from both the dermal and the inhalation exposure) can only be made with the assumption that both dermal and inhalation exposure contribute to the internal exposure every working day. The total internal occupational exposure of 1.2-1.5 mg Zn^{2+}/day (see **Table 4.12**) compared to the internal NOAEL of 10 mg Zn^{2+}/day results in MOSs of 6.7-8.3. Given the worst-case assumptions made, it is concluded that combined exposure to zinc chloride is of no concern for workers: **conclusion (ii)**.

4.1.3.2.5 Mutagenicity

Given the results from the mutagenicity studies, it is concluded that zinc chloride is of no concern for workers with regard to mutagenicity: **conclusion (ii).**

4.1.3.2.6 Carcinogenicity

There are no adequate carcinogenicity studies available. At the moment, there is no reason to require a carcinogenicity study: **conclusion (ii)**.

4.1.3.2.7 Toxicity for reproduction

There are no indications that Zn^{2+} caused adverse effects on fertility based on the results of the oral repeated-dose toxicity study in rats with zinc monoglycerolate: **conclusion (ii)**. Furthermore, there are no indications that Zn^{2+} is of concern for developmental effects based on the results of developmental toxicity studies in different species (mice, rats, hamsters and rabbits) and several studies in which pregnant women were exposed to soluble zinc compounds: **conclusion (ii)**.

4.1.3.2.8 Occupational Exposure Limits

The ACGIH established a TLV-TWA (1 mg/m^3) in 1968 and a STEL (2 mg/m^3) in 1976, which were revised in 1992 (see **Table 4.1**). The TWA was based on minimising the potential for respiratory irritation and pulmonary toxicity from occupational exposure to zinc chloride aerosols.

The documentation on the values established in The Netherlands, UK, Sweden and Denmark was not available.

From the data made available it is concluded that a concentration of 4.8 mg $ZnCl_2$/m^3 induced mild transient irritation of the respiratory tract in humans after a 30-minute exposure. Since these data already form the basis for the current occupational exposure limits, it is concluded that there is at present no need to reconsider the occupational exposure limits. However, a European OEL

is lacking but might be important as local effects lead to a conclusion (iii). The establishment of a European OEL should be considered.

4.1.3.3 Consumers

Table 4.13 Consumer exposure estimates

	Internal exposure (compound specific)	Internal exposure (not compound specific)
Zinc metal	negligible	
Zinc oxide	2.5 mg Zn^{2+}/day (5.1 including medically used zinc oil)	
Zinc chloride	0.2 mg Zn^{2+}/day	
Zinc sulphate	0.00046 mg Zn^{2+}/day	
Zinc phosphate	0.045 mg Zn^{2+}/day	
Zinc distearate	0.0062 mg Zn^{2+}/day	
Personal care products used regularly		1.6 mg Zn^{2+}/day

Only data on the use of zinc chloride in gargle are available. For this use, a consumer exposure of 0.2 mg zinc/day was calculated.

4.1.3.3.1 Acute toxicity/Irritation/Corrosivity/Sensitisation

Given the data available, the limited use of gargle and the resulting low exposure, it is concluded that zinc chloride is of no concern for consumers with respect to acute toxicity, skin, eye and respiratory tract irritation, corrosivity and skin sensitisation: **conclusion (ii)**.

4.1.3.3.2 Repeated dose toxicity

Starting point for the risk characterisation for systemic effects is the human oral NOAEL of 50 mg zinc/day. Assuming 20% absorption, this NOAEL corresponds to an internal dose of 10 mg zinc/day. The MOS between this (internal) NOAEL and the internal exposure by the use of gargle (0.2 mg/day) is 50.

However, consumer products containing zinc chloride are probably not used regularly. Besides, consumers can also be exposed to other zinc compounds in consumer products, some of which may be used on a regular basis (more than once a week). The use of regularly used products (dandruff shampoo, deodorant, eye shadow, and possibly baby care ointment) results in a cumulative (internal) exposure of approximately 1.6 mg zinc/day (see Section 4.1.1.3 and **Table 4.13**). Comparing the (internal) NOAEL with this more realistic exposure, a MOS of 6.25 can be calculated.

These MOSs are considered sufficient (see Section 4.1.3.1), and it can be concluded that there is no concern for consumers (**conclusion (ii)**), neither for zinc chloride nor for regularly used zinc compounds taken together.

4.1.3.3.3 Mutagenicity/Carcinogenicity/Toxicity for reproduction

Given the results from the mutagenicity studies, it is concluded that zinc chloride is of no concern for consumers with regard to mutagenicity: **conclusion (ii)**.

As there is no experimental or epidemiological evidence for carcinogenicity, there is no concern for carcinogenicity: **conclusion (ii)**.

Given the data available, it is concluded that zinc chloride is of no concern for reproductive toxicity: **conclusion (ii)**.

4.1.3.4 Humans exposed via the environment

4.1.3.4.1 Repeated dose toxicity

General exposure

For zinc, the ingestion of foods appears to be the most important exposure route for the general population, compared to which the intake by drinking water and ambient air is negligible. Recently, the average dietary intake of zinc is reported to be around 10 mg/day with a minimum of 0.6 mg and a maximum 39 mg. Both the reported average intake and the maximum intake are well below the human oral NOAEL of 50 mg/day and also well below the upper limit of safe intake as recommended by WHO (45 mg/day; 1996). Hence, it can be concluded that there is no concern for the general population exposed indirectly to zinc via the environment: **conclusion (ii)**.

Local exposure

Starting point for the risk characterisation for systemic effects are the local PEC_{add}s in air and water as presented in Section 4.1.1.4.2 and the human oral NOAEL of 50 mg zinc/day. Assuming 20% absorption, this NOAEL corresponds to an internal dose of 10 mg zinc/day. The local PEC_{add}s in air and water are converted to internal doses by correction for inhalatory and oral absorption (40% and 20%, respectively), and by assuming a breathing volume of 20 m^3/day and a drinking water consumption of 2 l/day (see **Table 4.14**).

Table 4.14 Internal exposure levels via water and air at local scale

	PEC_{add}-water (in µg/l)	Internal exposure (in mg zinc/day)	PEC_{add}-air (in µg/m^3)	Internal exposure (in mg zinc/day)
Production	45.6	0.018	0.0525	0.00042
Processing	3,154	1.3	3.2	0.026

Comparing the (internal) NOAEL with the internal exposures, MOSs are in the range 7.7-23,810. These MOSs are considered sufficient (see Section 4.1.3.1), and it can be concluded that there is no concern for human health (**conclusion (ii)**). Moreover, it must be noted that the internal exposures via water are overestimates. They are based on untreated surface water, which nowadays in the EU is not directly representative for drinking.

4.1.3.4.2 Mutagenicity/Carcinogenicity/Toxicity for reproduction

General and Local exposure

Given the results from the mutagenicity studies, it is concluded that zinc chloride is of no concern with regard to mutagenicity for the general population exposed indirectly to zinc via the environment: **conclusion (ii)**.

As there is no experimental or epidemiological evidence for carcinogenicity, there is no concern for carcinogenicity: **conclusion (ii)**.

Given the data available, it is concluded that zinc chloride is of no concern for reproductive toxicity: **conclusion (ii)**.

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

4.2.1 Exposure assessment

n.a.

4.2.2 Effects assessment: Hazard identification

4.2.2.1 Explosivity

Test data on explosive properties are not available. However, on theoretical considerations the substance is concluded not to be explosive.

4.2.2.2 Flammability

Test data on flammable properties are not available. However, on theoretical considerations the substance is concluded not to be flammable.

4.2.2.3 Oxidising potential

Test data on oxidising properties are not available. However, on theoretical considerations the substance is concluded not to be oxidising.

4.2.3 Risk characterisation

Given the physico-chemical data, zinc chloride is considered not to form a risk with respect to explosive, flammable and oxidising properties: **conclusion (ii)**.

5 RESULTS

5.1 ENVIRONMENT

n.a.

5.2 HUMAN HEALTH

5.2.1 Human health (toxicity)

5.2.1.1 Workers

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account

Acute local effects to the respiratory tract cannot be excluded in the occupational exposure scenario "production of zinc chloride".

It might be possible that in some industrial premises worker protection measures are already being applied.

Table 5.1 Overview of conclusions with respect to occupational risk characterisation

End point	Conclusions valid for the occupational scenarios					
	Scenario 1		Scenario 2 Galvanising		Scenario 2 Maintenance of flux baths[$]	
	MOS	Conclusion	MOS	Conclusion	MOS	Conclusion
Acute toxicity						
- dermal	n.a.	ii	n.a.	ii	n.a.	ii
- inhalation	≤ 309	ii	≤ 1,795 [a)] ≥ 3,571 [b)]	ii	≤ 7,900	ii
Irritation and corrosivity, single exposure						
- dermal	5	ii	7	ii	n.a.	ii
- inhalation	0.8	**iii**	4.4	ii	19	ii
- eyes	n.a.	ii	n.a.	ii	n.a.	ii
Sensitisation						
- dermal	n.a.	ii	n.a.	ii	n.a.	ii
- inhalation	n.a.	ii	n.a.	ii	n.a.	ii
Repeated dose toxicity, systemic effects						
- dermal	25	ii	33	ii	n.a.	ii
- inhalation	13	ii	8.3	ii	n.a.	ii
- combined	8.3	ii	6.7	ii	n.a.	ii
Mutagenicity	n.a.	ii	n.a.	ii	n.a.	ii
Carcinogenicity	n.a.	ii	n.a.	ii	n.a.	ii

Table 5.1 continued overleaf

Table 5.1 continued Overview of conclusions with respect to occupational risk characterisation

End point	Conclusions valid for the occupational scenario's					
	Scenario 1		Scenario 2 Galvanising		Scenario 2 Maintenance of flux baths[$]	
	MOS	Conclusion	MOS	Conclusion	MOS	Conclusion
Reproductive toxicity,						
Fertility	n.a.	ii	n.a.	ii	n.a.	ii
Developmental effects						
- dermal	n.a.	ii	n.a.	ii	n.a.	ii
- inhalation	n.a.	ii	n.a.	ii	n.a.	ii
- combined	n.a.	ii	n.a.	ii	n.a.	ii

n.a not applicable
[$] Exposure during maintenance of flux baths is not asumed to be of relevance for risk assessment after repeated exposure
a) For short-term inhalation exposure to $ZnCl_2$
b) For short-term inhalation exposure to ZnO
c) MOS based on an effect level

5.2.1.2 Consumers

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already

5.2.1.3 Humans exposed via the environment

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already

5.2.2 Human health (physico-chemical properties)

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already

Given the physico-chemical data, zinc chloride is considered not to form a risk with respect to explosive, flammable and oxidising properties.

6 REFERENCES

The reference list applies to zinc and the five zinc compounds and is included in the zinc metal document.

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ABBREVIATIONS

ADI	Acceptable Daily Intake
AF	Assessment Factor
ASTM	American Society for Testing and Materials
ATP	Adaptation to Technical Progress
AUC	Area Under The Curve
B	Bioaccumulation
BBA	Biologische Bundesanstalt für Land- und Forstwirtschaft
BCF	Bioconcentration Factor
BMC	Benchmark Concentration
BMD	Benchmark Dose
BMF	Biomagnification Factor
BOD	Biochemical Oxygen Demand
bw	body weight / *Bw*, *bw*
C	Corrosive (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
CA	Chromosome Aberration
CA	Competent Authority
CAS	Chemical Abstract Services
CEC	Commission of the European Communities
CEN	European Standards Organisation / European Committee for Normalisation
CEPE	European Committee for Paints and Inks
CMR	Carcinogenic, Mutagenic and toxic to Reproduction
CNS	Central Nervous System
COD	Chemical Oxygen Demand
CSTEE	Scientific Committee for Toxicity, Ecotoxicity and the Environment (DG SANCO)
CT_{50}	Clearance Time, elimination or depuration expressed as half-life
d.wt	dry weight / dw
dfi	daily food intake
DG	Directorate General
DIN	Deutsche Industrie Norm (German norm)
DNA	DeoxyriboNucleic Acid
DOC	Dissolved Organic Carbon
DT50	Degradation half-life or period required for 50 percent dissipation / degradation
DT90	Period required for 90 percent dissipation / degradation
E	Explosive (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)

EASE	Estimation and Assessment of Substance Exposure Physico-chemical properties [Model]
EbC50	Effect Concentration measured as 50% reduction in biomass growth in algae tests
EC	European Communities
EC10	Effect Concentration measured as 10% effect
EC50	median Effect Concentration
ECB	European Chemicals Bureau
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECVAM	European Centre for the Validation of Alternative Methods
EDC	Endocrine Disrupting Chemical
EEC	European Economic Communities
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EN	European Norm
EPA	Environmental Protection Agency (USA)
ErC50	Effect Concentration measured as 50% reduction in growth rate in algae tests
ESD	Emission Scenario Document
EU	European Union
EUSES	European Union System for the Evaluation of Substances [software tool in support of the Technical Guidance Document on risk assessment]
F(+)	(Highly) flammable (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
FAO	Food and Agriculture Organisation of the United Nations
FELS	Fish Early Life Stage
foc	Organic carbon factor (compartment depending)
GLP	Good Laboratory Practice
HEDSET	EC/OECD Harmonised Electronic Data Set (for data collection of existing substances)
HELCOM	Helsinki Commission -Baltic Marine Environment Protection Commission
HPLC	High Pressure Liquid Chromatography
HPVC	High Production Volume Chemical (> 1000 t/a)
IARC	International Agency for Research on Cancer
IC	Industrial Category
IC50	median Immobilisation Concentration or median Inhibitory Concentration
ILO	International Labour Organisation
IPCS	International Programme on Chemical Safety
ISO	International Organisation for Standardisation
IUCLID	International Uniform Chemical Information Database (existing substances)
IUPAC	International Union for Pure and Applied Chemistry
JEFCA	Joint FAO/WHO Expert Committee on Food Additives

JMPR	Joint FAO/WHO Meeting on Pesticide Residues
Koc	organic carbon normalised distribution coefficient
Kow	octanol/water partition coefficient
Kp	solids-water partition coefficient
L(E)C50	median Lethal (Effect) Concentration
LAEL	Lowest Adverse Effect Level
LC50	median Lethal Concentration
LD50	median Lethal Dose
LEV	Local Exhaust Ventilation
LLNA	Local Lymph Node Assay
LOAEL	Lowest Observed Adverse Effect Level
LOEC	Lowest Observed Effect Concentration
LOED	Lowest Observed Effect Dose
LOEL	Lowest Observed Effect Level
MAC	Maximum Allowable Concentration
MATC	Maximum Acceptable Toxic Concentration
MC	Main Category
MITI	Ministry of International Trade and Industry, Japan
MOE	Margin of Exposure
MOS	Margin of Safety
MW	Molecular Weight
N	Dangerous for the environment (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC
NAEL	No Adverse Effect Level
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NOEC	No Observed Effect Concentration
NTP	National Toxicology Program (USA)
O	Oxidizing (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
OC	Organic Carbon content
OECD	Organisation for Economic Cooperation and Development
OEL	Occupational Exposure Limit
OJ	Official Journal
OSPAR	Oslo and Paris Convention for the protection of the marine environment of the Northeast Atlantic
P	Persistent
PBT	Persistent, Bioaccumulative and Toxic

PBPK	Physiologically Based PharmacoKinetic modelling
PBTK	Physiologically Based ToxicoKinetic modelling
PEC	Predicted Environmental Concentration
pH	logarithm (to the base 10) (of the hydrogen ion concentration $\{H^+\}$
pKa	logarithm (to the base 10) of the acid dissociation constant
pKb	logarithm (to the base 10) of the base dissociation constant
PNEC	Predicted No Effect Concentration
POP	Persistent Organic Pollutant
PPE	Personal Protective Equipment
QSAR	(Quantitative) Structure-Activity Relationship
R phrases	Risk phrases according to Annex III of Directive 67/548/EEC
RAR	Risk Assessment Report
RC	Risk Characterisation
RfC	Reference Concentration
RfD	Reference Dose
RNA	RiboNucleic Acid
RPE	Respiratory Protective Equipment
RWC	Reasonable Worst Case
S phrases	Safety phrases according to Annex IV of Directive 67/548/EEC
SAR	Structure-Activity Relationships
SBR	Standardised birth ratio
SCE	Sister Chromatic Exchange
SDS	Safety Data Sheet
SETAC	Society of Environmental Toxicology And Chemistry
SNIF	Summary Notification Interchange Format (new substances)
SSD	Species Sensitivity Distribution
STP	Sewage Treatment Plant
T(+)	(Very) Toxic (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
TDI	Tolerable Daily Intake
TG	Test Guideline
TGD	Technical Guidance Document
TNsG	Technical Notes for Guidance (for Biocides)
TNO	The Netherlands Organisation for Applied Scientific Research
ThOD	Theoritical Oxygen Demand
UC	Use Category
UDS	Unscheduled DNA Synthesis

UN	United Nations
UNEP	United Nations Environment Programme
US EPA	Environmental Protection Agency, USA
UV	Ultraviolet Region of Spectrum
UVCB	Unknown or Variable composition, Complex reaction products of Biological material
vB	very Bioaccumulative
VOC	Volatile Organic Compound
vP	very Persistent
vPvB	very Persistent and very Bioaccumulative
v/v	volume per volume ratio
w/w	weight per weight ratio
WHO	World Health Organization
WWTP	Waste Water Treatment Plant
Xn	Harmful (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
Xi	Irritant (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)

Appendix A Internal NOAEL and minimal MOS calculation based on the NOAEL from the repeated dose study in the rat

Toxicological starting-point for the calculation of the internal NOAEL for systemic effects of Zn^{2+} due to $ZnCl_2$ exposure is the NOAEL of 31.52 mg zinc monoglycerolate/kg bw/day (corresponding with 13.3 mg Zn^{2+}/kg bw/day and 27.6 mg $ZnCl_2$/kg bw/day) from the 13-week study with rats. For oral absorption a value of 40% is used for the rat study (worst-case estimations) (see Section 4.1.2.1.6), resulting in an internal NOAEL of 5.3 mg Zn^{2+}/kg bw/d or 372 mg Zn^{2+}/day for a 70-kg worker.

The risk characterisation for systemic effects is made with several assumptions:

- the internal NOAEL is calculated with worst-case assumptions for oral absorption,
- it is assumed that other factors influencing route-specificity are not of importance. In case of Zn^{2+}, metabolism does not play a role, which favours this assumption,
- the study was not performed with $ZnCl_2$, so it is assumed that the effects are due to Zn^{2+},
- the background intake and requirement of zinc in the experimental situation (rats) and in workers are assumed to be comparable,
- the physiological role of zinc is comparable between rat and man.

Dermal and inhalation exposure

Given the estimated frequency of dermal and inhalation exposure chronic exposure is assumed for respiratory risk characterisation.

The assessment factors applicable for the calculation of the minimal MOS are mentioned in **Table A.1**.

Table A.1 Assessment factors applied for the calculation of the minimal MOS

Aspect	Assessment factors applied on oral NOAEL
Interspecies differences	4 · 3 a)
Intraspecies differences	3
Differences between experimental conditions and exposure pattern of the worker	10
Type of critical effect	1
Dose-response curve	1
Confidence of the database	1 b)
Overall	360

a) Extrapolation based on differences in caloric demands, together with a factor 3 for remaining uncertainties.
b) Database exists of the available toxicological studies with zinc and zinc compounds.

The minimal MOS amounts to 360 when the 13-week oral toxicity study in rats with zinc monoglycerolate is taken as a starting point for the risk characterisation for repeated dose toxicity.

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Zinc chloride, Volume 45

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Environment and quality of life series

The report provides the comprehensive risk assessment of human health part of the substance zinc choride. It has been prepared by the Netherlands in the frame of Council Regulation (EEC) No. 793/93 on the evaluation and control of the risks of existing substances, following the principles for assessment of the risks to humans and the environment, laid down in Commission Regulation (EC) No. 1488/94.

The evaluation considers the emissions and the resulting exposure to the environment and the human populations in all life cycle steps. Following the exposure assessment, the environmental risk characterisation for each protection goal in the aquatic, terrestrial and atmospheric compartment has been determined. For human health the scenarios for occupational exposure, consumer exposure and humans exposed via the environment have been examined and the possible risks have been identified.

The human health risk assessment for zinc chloride concludes that there is concern for workers. For consumers and humans exposed via the environment, the risk assessment concludes that risks are not expected.

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