European Chemicals Bureau

Institute for Health and Consumer Protection

European Chemicals Bureau

Existing Substances

European Union Risk Assessment Report

CAS No: 1314-13-2

EINECS No: 215-222-5

zinc oxide

ZnO

European Union Risk Assessment Report

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European Union Risk Assessment Report

ZINC OXIDE

Addendum to the Part II (Human Health) – 2004

CAS No: 1314-13-2

EINECS No: 215-222-5

RISK ASSESSMENT

EXPLANATORY NOTE

This report is an addendum to the European Risk Assessment Report (RAR) on zinc oxide, (part II, Human Health) that has been prepared by the Netherlands in the context of Council Regulation (EEC) No. 793/93 on the evaluation and control of existing substances and published in 2004 on the European Chemicals Bureau website (European Risk Assessment Report Vol. 43, EUR 21171 EN) [1].

In the frame of this work, the initial human health risk assessment for zinc oxide was updated with new dermal exposure data, which led to changes in the conclusions on dermal exposure estimates for zinc oxide. Results are presented in this addendum.

For detailed information on the risk assessment principles and procedures followed, the underlying data and the literature references the reader is referred to the comprehensive Final Risk Assessment Report (Final RAR).

[1] European Chemicals Bureau – Existing Chemicals – http://ecb.jrc.it

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TABLES

DERMAL EXPOSURE OF WORKERS TO ZINC COMPOUNDS IN PRODUCTION AND USE

1 INTRODUCTION

Since the human exposure part of the Risk Assessment Report has been discussed and agreed at the Existing Substances Regulations Technical Meeting, relevant new dermal exposure data have been presented. These data lead to changes in the conclusions on dermal exposure estimates for zinc oxide. The dermal exposure estimates in the present Risk Assessment Reports are based on measurements of exposure to zinc for workers producing zinc dust and zinc oxide and measurements of exposure to calcium carbonate for workers producing paints (dumping powders). The new data concern the maximum skin adherence after immersion of zinc oxide and of zinc dust and new exposure measurements for dumping of zinc oxide.

Conclusions for scenario-specific exposure estimates

Zinc oxide

It is concluded that dermal exposure was overestimated and needs reconsideration in the following occupational exposure scenarios:

- Scenario 1: Production of zinc oxide;
- Scenario 2: Production of paint (and some other products) containing zinc oxide;
- Scenario 3: Use of zinc oxide in the rubber industry.

The new reasonable worst-case dermal exposure estimates are:

- Scenario 1: 1,880 mg zinc oxide/day (1504 mg zinc/day);
- Scenario 2: 500 mg zinc oxide/day (400 mg zinc/day);
- Scenario 3: 500 mg zinc oxide/day (400 mg zinc/day).

The new typical case dermal exposure estimates are:

- Scenario 1: 728 mg zinc oxide/day (582 mg zinc/day);
- Scenario 2: 200 mg zinc oxide/day (160 mg zinc/day);
- Scenario 3: 200 mg zinc oxide/day (160 mg zinc/day).

No changes are needed for the exposure estimates of other scenarios for zinc oxide.

Other zinc compounds

The available data do not indicate what physico-chemical parameter(s) are relevant determinants for dermal exposure or for maximum adherence to the skin. Therefore, the estimates for other zinc compounds, which are based on higher values for other substances than the values now concluded for zinc oxide, will not be changed.

Conclusions to risk characterization for workers

Zinc oxide

Because it is concluded that dermal exposure was overestimated in Scenarios 1 to 3, the MOS values for the new exposure estimates were reassessed for scenarios of concern among these, i.e.

having a **conclusion (iii)**. This only concerns Scenario 1 for repeated dose toxicity, combined exposure.

Based on a calculated internal NOAEL of 10 mg Zn^{2+}/day and a minimal MOS of 1 (see Section 4.1.3.1), it is concluded that the internal occupational exposures of 6.2 – 11.6 mg Zn^{2+}/day for Scenario 1 result in a **conclusion (ii)**, as they are considered not significantly lower than the minimal MOS, i.e. by comparing MOS and minimal MOS values. In the Risk Assessment Report only workplace 4 of this scenario with an internal dose of 13 mg Zn^{2+}/day was considered of concern, whereas production and recycling activities with internal doses of 12.2 mg Zn^{2+}/day were considered of no concern. With the new exposure data all internal doses are below 12.2 mg Zn^{2+}/day (and consequently not associated with concern).

Thus, with respect to the seven identified worker exposure scenarios with zinc oxide, Scenario 4 "use of paint containing zinc oxide" is still of concern, i.e. a **conclusion (iii)** is still valid.

Below the concerning section of the Risk Assessment Report, i.e. the repeated dose toxicity section for combined exposure on pages 103-104, is presented.

2 REVISED RISK CHARACTERISATION

4.1.3.2 Workers

4.1.3.2.5 Repeated dose toxicity

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 1.2-14 mg Zn^{2+}/day (see **Table 4.17**) compared to the internal NOAEL of 10 mg Zn^{2+}/day results in a **conclusion (iii)** for Scenario 4 (use of paint containing zinc oxide) (calculated MOS value 0.7). Based on the typical exposure estimates for inhalation exposure, adverse health effects cannot be excluded in Scenario 4.

It is noted, though, that these estimates are considered conservative values and will probably overestimate real exposure levels to an unknown extent.

Table 4.17 Occupational risk assessment of zinc oxide for repeated dose toxicity after combined dermal and inhalation exposure

	Risk characterisation for dermal and inhalation exposure			
Scenario / subscenario#	**Estimated internal dermal exposure in mg Zn^{2+}/day a)**	**Estimated internal inhalation exposure in mg Zn^{2+}/day a)**	**Combined internal exposure in mg Zn^{2+}/day**	**MOS b)**
1: Production	3.0	-	-	-
- Production c)		7.8	10.8	0.9
- Recycling		7.8	10.8	0.9
- Workplace 1		3.4	6.4	1.3
- Workplace 2		3.2	6.2	1.3
- Work place 3		3.2	6.4	1.3
- Work place 4		8.6	11.6	0.9
2: Production of paints containing zinc oxide	0.8	4	4.8	2.1
3: Production of rubber products containing zinc oxide	0.8	0.6	5.0	2
4: Use of paint containing zinc oxide	10.8	3.2	1.4	7.1
5: Zinc die casting	0.3	1.6	1.9	5.3
6: Brass casting - Full shift	0.3	3.2	3.5	2.9
7: Welding of zinc coated steel	Negl.	1.2	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 dumping and spraying. It is noted that possible higher risks resulting from daily performance of these activities associated with higher short-term exposures, are not accounted for.

a) See Table 4.15 in the comprehensive Risk Assessment Report for derivation of internal exposure values.

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

c) All data, except recycling, combined.

Summary of new exposure data

The new results can be summarised as follows.

Measurements were done by Hughson and Cherrie (2002) in experimental settings to establish:

- the maximum skin surface loading on hands and forearms of zinc oxide and zinc dust (n = 6); this was done by immersing hands completely in the powder while rubbing the hands to ensure complete contact with the powder;
- the accumulation of skin surface loading of zinc oxide on the hands after hand press contact with a contaminated surface after 1, 2, 4 and 8 contacts (n = 6);
- the accumulation of skin surface loading of zinc oxide on the hands and forearms due to dumping 1, 2, 4 and 8 bags of zinc oxide (n = 4).

The methods of sampling and analysis were the same as in the earlier study by the same authors: wipe sampling at three moments over the shift and pooling the samples per part of the skin per worker into one sample before analysis.

The results are presented in **Table 1** below:

Table 1 Results of the study by Hughson and Cherrie (2002)

Parameter	Substance	Result (range in µg/cm²)	Remark
Maximum skin surface loading after immersion (hands only)	Zinc oxide	390-940	Zinc oxide is substantially less dusty than zinc dust
Maximum skin surface loading after immersion (hands only)	Zinc dust	3750-6410	Zinc oxide is substantially less dusty than zinc dust
Skin surface loading after hand press contact (hands only)	Zinc oxide	88-438	No relation observed with number of contacts
Skin surface loading after dumping of 1 or 2 bags (hands and forearms)	Zinc oxide	16-70	Result for hands only = 26-56 µg/cm²
Skin surface loading after dumping of 4 bags (hands and forearms)	Zinc oxide	14-97	Result for hands only = 20-157 µg/cm²
Skin surface loading after dumping of 8 bags (hands and forearms)	Zinc oxide	64-184	Result for hands only = 76-230 µg/cm²

Measurements were done by RISKOFDERM (2003) in the rubber industry. Workers opening and emptying bags of zinc oxide into hoppers and mixers were studied. The process generally consisted of picking up a bag, lifting it to the height of the dumping opening, cutting it open with a knife, dumping the contents of the bag into the hopper or mixer and discarding the empty bag (generally in some kind of container).

Measurements were done in three factories with approximately 40, 150 and 300 workers. In each of the factories four workers were sampled. One factory was visited on four separate days, while the other two factories were visited on two separate days each.

The duration of measurement (and dumping for one batch) was between 2.5 and 11 minutes (mean: 5.7 minutes). In this period between 2 and 20 bags (25 kg per bag) of zinc oxide was dumped. The amount of zinc oxide dumped was therefore between 50 and 500 kg (mean: 281).

Measurements of hand exposure were done using a hand washing technique (recovery from skin not tested). Exposure to the whole body was measured using cotton coveralls.

The results of these measurements are presented in **Table 2** below.

Table 2 Dermal exposure (rate) during loading of zinc oxide into hoppers and mixers

Exposure of hands or body to zinc	Range (mg)	AM (mg)	SD (mg)	GM (mg)	GSD	AM (µg/cm²)	GM (µg/cm²)	AM (µg/cm²/ min)	GM (µg/cm²/ min)
Hands Zinc	21-122	56	35	47	1.81	68	57	15	11
Hands Product (zinc oxide)	24-147	66	42	55	1.82	80	68	18	13
Whole body Zinc	47-1,199	391	400	238	2.93	19	12	4.3	2.3
Whole body Product (zinc oxide)	55-1,403	459	468	281	2.93	23	14	5.1	2.7

* For the calculations of the concentration on the skin, in µg/cm², a surface area of 820 cm² was assumed for the hands.

** For the calculations of the concentration on the skin, in µg/cm², a surface area of 20,290 cm2 for the total body was assumed, according to the sum of the measured areas.

Discussion

The new data clearly show that some physico-chemical parameters of the substance influence the maximum adherence of dust of the substance to the skin. The relations between physico-chemical parameters, maximum adherence to the skin and dermal exposure levels in practical situations can clearly not be established based on the available data. Therefore, conclusion for other substances than zinc oxide cannot be changed, because all relevant new data are for zinc oxide, except for the maximum adherence to the skin of zinc metal dust.

Hughson and Cherrie (2002) in their summary conclude: "*Overall, the laboratory tests provide reassurance that the workplace samples were not significant overestimates of exposure. However, the repeat contact tests do suggest that the rate of dust loading, at least for zinc oxide, quickly tended towards a level that did not change with further activity. We believe this means that a measure of exposure based on an accumulation of sequential wipe samples would be equivalent to a practical maximum level of exposure, whereas an average of the individual samples would be our 'best estimate' of average dermal exposure.*"

The conclusions in the Risk Assessment Report for production of zinc oxide (Scenario 1) are in the order of 1,400 µg/cm^2 (zinc oxide). This does appear to be high compared to the maximum adherence value of 940 µg/cm^2 (zinc oxide) found in the study by Hughson and Cherrie (2002). The value of 1,400 µg/cm2 (zinc oxide) was based on repeat sampling throughout the day, where the samples were pooled before analyses. This may have led to an overestimate of the real dermal exposure levels. On the other hand, the workplace situation may include parameters that increase the maximum adherence, such as humidity of the hands due to working part-time with gloves on, sweating, etc. Furthermore, the dermal exposure levels in zinc oxide manufacturing and zinc dust manufacturing in the original study by Hughson and Cherrie (2001) are not clearly different. This may be explained by several possible explanations that cannot be concluded upon, e.g.:

- the maximum adherence to the skin (as established by Hughson and Cherrie (2002) is not a very important parameter for dermal exposure assessment;
- the maximum adherence to the skin is highly dependent on the person and may be (much) higher than established by Hughson and Cherrie (2002);
- the circumstances may influence both the substance and the skin and therefore influence the maximum adherence to the skin;
- different grades or variations of zinc oxide may have a different maximum adherence to the skin and may lead to a different dermal exposure level;
- the workers in the study by Hughson and Cherrie (2001) were not only exposed to zinc oxide, but also to zinc dust (or other zinc compounds);

In their discussion regarding the new experiments, Hughson and Cherrie (2002) suggest that the repeated sampling did lead to overestimation of the real values and that: "*Our 'best estimate' dermal exposures are an average measurement obtained by applying a factor of 1/3 to the original data. This is to account for the accumulation of 3 separate samples for each measurement.*" This is a reasonable suggestion if the three measurement periods lead to approximately the same skin surface loading and/or if one-third of the accumulated value is close to the maximum adherence to the skin. The first condition cannot be tested and is not necessarily met in this case. It is possible that almost all of the measured contaminant came from one of the wipe sampling periods. The second condition may be relevant for zinc oxide, but would certainly not be relevant for zinc dust, which has a maximum adherence about 10 to 20 times the value calculated by dividing the accumulated dermal exposure value by three. To account for the probable effect of the maximum adherence of zinc oxide and the possibility of overestimation due to repeat sampling (that is clearly higher if the maximum adherence is exceeded), it is concluded that the maximum adherence as measured by Hughson and Cherrie (2002) will be used as the basis for the estimation of dermal exposure to zinc oxide in production of zinc oxide. This leads to an estimated reasonable worst-case dermal exposure estimate of 940 $\mu g/cm^2 \cdot 2{,}000\ cm^2$ = 1,880 mg zinc oxide/day (1,504 mg zinc/day). For the typical value, the highest "best estimate" as calculated by Hughson and Cherrie (2002) will be used as a basis for the assessment. This estimate is the highest accumulated skin surface loading, divided by three. Multiplying this value with the skin surface area exposed leads to a typical dermal exposure estimate for production of zinc oxide of 364 $\mu g/cm^2 \cdot 2{,}000\ cm^2$ = 728 mg zinc oxide/day (582 mg zinc/day).

The data by both Hughson and Cherrie (2002) and by RISKOFDERM (2003) show that both skin surface loading and dermal exposure levels for dumping of zinc oxide are clearly lower than the estimates based on measurements of calcium carbonate. Therefore, the new data will be taken as a basis for the assessment for Scenarios 2 and 3. The three studies with repeated bag dumping do not give a clear answer regarding the accumulation with increasing number of bags dumped. Hughson and Cherrie (2002) and Lansink et al. (1996) find a higher skin surface loading with higher numbers of bags. RISKOFDERM (2003) did not find a relation between skin surface loading and number of bags dumped. Therefore a limited influence of this factor is considered plausible. This is accounted for by using a rounded value of the highest skin surface loading for hands from Hughson and Cherrie (2002; 0.25 mg/cm^2) and multiplying this with the full surface of hands and forearms. This leads to a reasonable worst-case dermal exposure level of 500 mg zinc oxide/day (400 mg zinc/day) for dumping of zinc oxide, both for Scenario 2 and for Scenario 3. For the typical case, a rounded value of 100 $\mu g/cm^2$ (zinc oxide) will be used for surface loading, being approximately the average of the average values found for surface loading of hands by Hughson and Cherrie (2002; 130 $\mu g/cm^2$) and by RISKOFDERM (2003;

80 μg/cm^2). This leads to an estimated typical dermal exposure level of 200 mg zinc oxide/day (160 mg zinc/day).

3 REFERENCES

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European Union Risk Assessment Report

ZINC OXIDE

Part II – Human Health

CAS No: 1314-13-2

EINECS No: 215-222-5

RISK ASSESSMENT

Cataloguing data can be found at the end of this publication

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ZINC OXIDE

Part II – Human Health

CAS No: 1314-13-2

EINECS No: 215-222-5

RISK ASSESSMENT

Final Report, 2004

The Netherlands

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.

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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[2] 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.

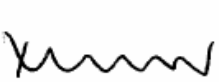
There are four overall stages in the Regulation for reducing the risks: data collection, priority setting, risk assessment and risk reduction. Data provided by Industry are used by Member States and the Commission services to determine the priority of the substances which need to be assessed. For each 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[3], which is supported by a technical guidance document[4]. 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 Health and Environmental Risks (SCHER) 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 c



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[2] O.J. No L 084, 05/04/1993 p.0001 – 0075

[3] O.J. No L 161, 29/06/1994 p. 0003 – 0011

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

0 OVERALL RESULTS OF THE RISK ASSESSMENT

CAS No: 1314-13-2
EINECS No: 215-222-5
IUPAC Name: Zinc oxide

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.

This conclusion is reached, because:

- metal fume fever due to acute inhalation exposure cannot be excluded in occupational exposure scenario 7 (welding of zinc coated steel);
- systemic effects after repeated dermal exposure at the workplace cannot be excluded in Scenario 4 (use of paint containing zinc oxide). Besides, health risks due to combined exposure in Scenario 1 (production of zinc oxide; recycling; work place 4) and Scenario 4 cannot be excluded too.

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.

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TABLES

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS No: 1314-13-2
EINECS No: 215-222-5
IUPAC name: zinc oxide
Synonyms: zinc white
Molecular formula: ZnO
Structural formula: ZnO
Molecular weight: 81.38

1.2 PURITY/IMPURITIES, ADDITIVES

Purity: > 93%
Impurity: According to the companies several impurities might occur:

Table 1.1 Impurities in zinc oxide

Impurity*	CAS No.	Quantity (% w/w)
Water		< 4
Zinc carbonates		< 2
Iron oxide (as iron)	7439-89-6	< 0.2
Lead oxide (as lead)	1317-36-8	< 0.5
Cadmium oxide (as cadmium)	7440-43-9	< 0.07

* Different impurities may be found in different batches and are depending on the process

Additives:

Table 1.2 Additives in zinc oxide

Additive*	CAS No.	Quantity (%w/w)
Distillates (naphthenic mineral oils)		0.2-5
Blends of inorganic compounds		0.2-4
Blends of aliphatic or aromatic carboxylic acids		0.2-2

* Different additives may be found in different batches

1.3 PHYSICO-CHEMICAL PROPERTIES

In **Table 1.3** the physico-chemical properties are summarised.

Table 1.3 Physico-chemical properties of zinc oxide

Property	Result	Comment
Physical state	solid, powder	*
Melting point	> 1,975°C (high pressure)	**
Boiling point	not applicable	****
Relative density	5.6	*
Vapour pressure	not applicable	***
Surface tension	not applicable	****
Water solubility	< 1.6 mg/l	+
Solubility in other solvents	insoluble in alcohol; soluble in acids	*
Partition coefficient n-octanol/water (log value)	not applicable	****
Flash point	not applicable	****
Flammability	not flammable	****
Auto flammability temperature	not applicable	****
Explosive properties	not explosive	****
Oxidising properties	not oxidizing	****
Granulometry	particle size: 100-10,000 nm	*****

* More than one apparently independent source. No methods are specified.
** Several values found in literature. Sublimation will occur at temperatures lower than melting temperature.
*** Not relevant at ambient temperature.
**** Conclusion based on theoretical, and/or structural considerations.
***** Several values found in literature, all in the same range.
\+ Solubility depending on mass loading and type of water medium (LISEC-REPORT, 1997).

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

Conclusion

Data on boiling point, vapour pressure, 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. Information on flammability, explosive properties and oxidising properties is not available. However, on theoretical considerations the compound is concluded to be not flammable, not explosive and not oxidising. 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 fulfill the Annex VIIA requirements.[5]

[5] Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. OJ No P 196, 16/08/1967, p. 0001-0098.

1.4 CLASSIFICATION

Current classification according to Annex I

In the proposal of the 29th ATP of Directive 67/548:

N; R50-53 Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment

S phrases

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

Decision of the CMR Working Group

At the September 2002 meeting, it was agreed not to classify zinc oxide for physical chemical properties and health effects.

2 GENERAL INFORMATION ON EXPOSURE

(to be added later)

3 ENVIRONMENT

(to be added later)

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.1 General discussion

Zinc oxide is an important rubber compounding material (Kirk-Othmer, 1982d). It is used in all types of rubber, which are cross-linked with sulphur. A further major use of zinc oxide is in glass and ceramic products. Zinc oxide absorbs ultraviolet light, and is used as a sunscreen in pharmaceutical and cosmetic products. It is also used to wound healing as a bacteriostat in medical plasters and in baby creams and calamine lotion. In paints, zinc oxide is mainly used as a corrosion inhibitor and to a lesser extent as a mildew stat. Zinc is a trace element, essential to life and zinc oxide is one of the main means of zinc addition in fertilisers, animal feeds and human vitamin supplements. In combination with eugenol it is used in dental cement. Finally zinc oxide acts as a catalyst in alkylation, oxidation, hydrogenation and desulphurisation reactions (ZOPA, 1998a). The dustiness of zinc oxide has been tested by a modified Heubach method. The total dustiness was found to be 30 mg/g with 84.53% larger than 8.13 μm and 73.92% larger than 15.8 μm (Deutsche Montan Technologie, 2000).

Occupational limit values

In several countries there are occupational limit values for zinc oxide fumes and for dust (see **Table 4.1**). Dust exposure is relevant for occupational exposure scenarios when commercial grades of zinc oxide are handled.

Table 4.1 Occupational limit values for zinc oxide

Country / organisation	8-hour TWA (mg/m^3)	15-min STEL (mg/m^3)	References
USA	5 (fumes [1]) 10 (dust [2])	10 (fumes) (ceiling)	ACGIH (1991) (guidance values)
USA	5 (fumes) 15 (dust; total) 5 (dust; respirable)		OSHA (1989) (legal limit values)
The Netherlands	5 (fumes)	-	SZW (1997)
Germany [3)]	5 (fumes) 6 (dust)		DFG (1997)
UK	5 (fumes) 10 (dust)	10	HSE (1998)

Table 4.1 continued overleaf

Table 4.1 continued Occupational limit values for zinc oxide

Country / organization	8-hour TWA (mg/m^3)	15-min STEL (mg/m^3)	References
Sweden	5 (fumes)		National Board of Occupational Safety and Health, Sweden (1993)
Denmark	4 (fumes) 10 (dust)		Arbejdstilsynet (1992)

1) Operational definition for this risk assessment: zinc fumes are formed from volatilised zinc/zinc oxide by condensation. Ultra fine fume (diameter < 0.1 microns) is known to be generated only in operations involving cutting or welding of galvanised structures, where the zinc coating will be subjected to a flame temperature of close to 1,000ºC.
2) Operational definition for this risk assessment: zinc dust is defined as particles of zinc with an average diameter of > 0.1 microns.
3) Fumes measured as respirable aerosols

4.1.1.2 Occupational exposure

Exposure to zinc oxide will mainly take place in the workplace by means of the inhalation and by the dermal route. Exposure due to the handling of solid zinc oxide is in the form of dust. However, relevant exposure to zinc oxide is also possible in several situations where zinc oxide is formed from volatilised molten zinc compounds by oxidation with the oxygen in the air. This emission is in the form of metal fumes which are usually measured as dust ("total" or "respiratory") and the zinc content of these fumes is usually analysed and calculated as elementary zinc or zinc oxide. In the metal fumes zinc is not present in its elementary form because the oxidation kinetics is very fast and it is very unlikely that metallic zinc vapour can exist for a measurable period. Fumes have a much smaller particle size than dusts. Actual exposure is in most situations exposure to coagulated aerosols and not to very fine dusts.

Dermal exposure may occur as part of the usual work task (e.g. formulation and the use of products containing zinc oxide) or may take place when maintenance of machinery is necessary.

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 harmonized European legislation.

Knowledge of effectivity of PPE in practical situations is very limited. Furthermore, the effectivity 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.

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.

Based on the production and use categories of zinc oxide the following scenarios for exposure to zinc will be discussed:

Scenario 1: Production of zinc oxide
Scenario 2: Production of paint containing zinc oxide
Scenario 3: Production of rubber goods containing zinc oxide
Scenario 4: Use of paint containing zinc oxide
Scenario 5: Zinc die-casting
Scenario 6: Brass casting
Scenario 7: Exposure to zinc oxide during welding

For each scenario the general description of measured exposure data will be followed by the use of suitable models to calculate inhalation and dermal exposure. The used methods will be compared using expert judgement and a choice for the best applicable estimators will be made.

4.1.1.2.1 Scenario 1: Production of zinc oxide

Zinc oxide is produced by direct and indirect processes. Occupational exposure to zinc oxide is possible due to oxidation of zinc that possibly escapes from furnaces and due to the emission of zinc oxide from parts of the process when zinc oxide is already formed. An important task that may lead to contamination of the facility and to exposure (direct or indirect) of workers is the packaging and repackaging of the produced zinc oxide in bags, big bags or bulk tankers.

Measured data on zinc oxide

A number of exposure data has been provided by industry (ZOPA, 1998b; several zinc companies, 1999; Groat et al., 1999; EBRC, 2000). Exposure levels are sometimes mentioned without sufficient detail, such as duration of measurements, measurement methods and strategies. Generally, no data on worker activities during measurements are given. Also it is sometimes not clear whether the data refer to personal monitoring or to stationary measurements. Four companies have presented data in amounts Zn/m^3 with levels of 0.3-1.7 mg Zn/m^3; two companies have presented data on total dust (< 1 and 2.6 mg/m^3) and respirable dust (< 1 and 0.8 mg/m^3) and five companies have presented data in amounts ZnO/m^3 (0.28-2.95 mg/m^3). It is assumed that the data refer to full-shift exposure. Several values are presented as single values. It is assumed that these are either averages or results of single measurements. It is assumed that the exposure levels all relate to aerosols with relatively large particle sizes (1 μm and upwards), though there is in the above mentioned data sets no information on the measurement method.

Recent measurements in one zinc oxide producing company were reported by Groat et al. (1999). Measurements were done to study the particle size distribution, but total inhalation exposure levels were also calculated. Total inhalation amounts of zinc were measured by personal, full-shift sampling for 7 workers and 2 short-term measurements were also done during bagging and during cleaning around the indirect furnace. The full-shift exposure levels were between 1.6 and 3.8 mg zinc/m^3 and the short-term levels (< 1 hour) were 1.3 and 2.1 mg zinc/m^3. Assuming that all zinc is in the form of zinc oxide, the maximum measured exposure level expressed as ZnO was approximately 4.7 mg/m^3. The particle size distribution as determined by Groat et al. (1999) shows that between 26 and 74% of the sampled dust is larger than 21.3 μm, 73-95% is larger than 3.5 μm and only < 1-5% is smaller than 0.52 μm, where the value close to 5% was reached in a short-term measurement and all other values were below 2%.

The exposure level for very fine particles (< 0.52 μm) is therefore below 2% of 4.7 mg/m^3, being < 0.1 mg/m^3.

By the EBRC (2000, 2001a), a questionnaire was sent to all producers of zinc oxide for collection of data to construct an inhalation exposure database for this industry. The data received were grouped in the following categories:

Workplace 1: raw material delivery discharge, transportation, storage and preparation of raw material,
Workplace 2: area of furnace/kiln, charging of kiln,
Workplace 3: maintenance of furnace,
Workplace 4: further processing of finished zinc oxide (packaging, bagging etc.).

The final report (EBRC, 2001a) is based on data received from 14 (out of 18) producers in Europe. The data are based partly on static sampling and partly on personal sampling, measured over the job duration time, which may be assumed to be representative for full-shift exposures. In the final report, two companies with high values and their influence on the total results are also considered separately. One company is in fact a recycling company, not a zinc oxide producer. The other company is rather small, so it is not possible to allocate workers to a main workplace. Excluding the recycling company, the median of the data (n = 181) is 0.85 mg/m³, and the 90th percentile is 3.9 mg/m³.

These data were extended with measured data from another company The two recycling companies (n = 21) showed a median value of 0.9 mg Zn/m^3 and a 90th percentile of 3.9 mg Zn/m^3.

The analysis by workplace is mentioned in **Table 4.2**. In the analysis both the recycling company and the small company are omitted.

Table 4.2 Exposure during zinc oxide production (with and without exclusion of outliers)

Workplace	Number of samples	Median values (mg Zn/m^3)	90th Percentiles (mg Zn/m^3)
Category 1	8	0.4	1.7
Category 2	54	0.6	1.6
Category 3	12	0.6	1.6
Category 4	86	0.8	4.3

Data on respirable particles were discounted in view of particle size considerations, because they underestimate total exposure. These data show that the level of exposure to zinc oxide in this fraction is negligible.

Dermal exposure data for zinc oxide production are also available. 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 (see **Table 4.3**).

In Survey 1, a zinc oxide production plant was studied. In Survey 2, two plants producing zinc dust and zinc oxide and one plant producing zinc oxide only were studied. Hughson and Cherrie (2001) cluster the results in results for tasks with intermittent direct handling and results for tasks with extensive direct handling. This is done for comparison with EASE. In this risk assessment report the results are, however, clustered per job or task name, with all workers performing a task called "packing", "blending", "pelletising" or "classifying" in the group "high-exposure task" and all others in the group "low-exposure task". The division in tasks could only be made for plants B and D in the second survey, since the workers in the plant in the first survey and those in plant A in the second survey only had more general tasks (e.g. "operator"). For plants A and B also a clustering of zinc and zinc oxide workers is made.

Results are summarised in **Table 4.3**.

Table 4.3 Results of the measurement of zinc exposure levels (mg zinc) in plants producing zinc oxide and/or zinc dust (Hughson and Cherrie 2001)

Result	n	Minimum	Maximum	GM	GSD	Remarks
Survey 1 hands and forearms	15	41.3	587.2	158.6	2.6	zinc oxide plant; for one worker the value for whole body was equal to the value for hands and forearms because of missing samples
Survey 1 whole body	15	57,8	722,1	251,9	2.2	
Survey 2 hands and forearms	10	141	1,005	513	1.8	all workers plant A
	6	*232*	*1,005*			*zinc oxide workers plant A*
	4	*141*	*812*			*zinc dust workers plant A*
Survey 2 whole body	10	160	1,125	637	1.7	all workers plant A
	6	*569*	*1,125*			*zinc oxide workers plant A*
	4	*160*	*822*			*zinc dust workers plant A*
Survey 2 hands and forearms	8	315	2,216	906	2.2	all workers plant B, except a worker with a missing sample for the forearm
	2	*315*	*340*			*furnace operators plant B*
	2	*4,448*	*2,216*			*zinc oxide high-exposure (packing) plant B*
	4	*901*	*1,911*			*zinc dust high-exposure plant B*
Survey 2 whole body	7	413	2,682	1,094	2.2	all workers plant B, except two workers with missing samples
	2	*413*	*520*			*furnace operators plant B*
	2	*553*	*2,378*			*zinc oxide high-exposure (packing) plant B*
	3	*1,118*	*2,682*			*zinc dust high-exposure plant B*
Survey 2 hands and forearms	11	121	2,157	472	2.8	all workers plant D
	6	*121*	*401*			*plant D low-exposure group*
	5	*419*	*2,157*			*plant D high-exposure group*
Survey 2 whole body	11	135	2,369	541	2.7	all workers plant D
	6	*135*	*565*			*plant D low-exposure group*
	5	*439*	*2,369*			*plant D high-exposure group*

In general, the exposure was mostly to hands and forearms. However, some workers had considerable exposure of the head/face, neck and/or chest as well.

Task specific exposures were measured 6 times. The results are mentioned in **Table 4.4**.

Table 4.4 Task specific dermal exposures to zinc measured in zinc powder (oxide and dust) production facilities

Job description	Facility	Dermal exposure (µg zinc/cm²) on hands and forearms
Manual IBC emptying	A	202
Manual IBC emptying	A	319
ZnO packing – 25 kg sacks	B	389
IBC changeover	D	130
ZnO packing – 25 kg sacks	D	49
ZnO packing – 25 kg sacks	D	27

Models

The production of zinc oxide takes place in mostly closed systems. Exposure will mainly take place during packaging, cleaning and maintenance. It is assumed that these activities will take place at room temperature. The vapour pressure of zinc oxide is negligible at this temperature. Aerosol formation will take place during packaging only. Exposure during packaging is estimated, using EASE, to be 2-5 mg/m^3 (dry manipulation and LEV; TGD, 1996).

During packaging, which is drumming in bags, big bags, or road containers, use is intermittent, non-dispersive and the exposure will be mainly to the palms of both hands (420 cm^2). Dermal exposure is estimated to be 0.1 to 1 mg/cm^2/day, leading to a maximum of 420 mg/day. Exposure due to drumming in 25 kg bags is expected to be higher than due to drumming in big bags, because of the more direct handling of the (filled) bags.

Conclusions

Inhalation exposure

The number of measured data is relatively large. Based on all measured data, except the values of the recycling company, the 90th percentile will be taken as a reasonable worst-case value: 3.9 mg Zn/m^3. For the typical value, the median will be taken: 0.85 mg/m^3. For the recycling companies, these values are 3.9 and 0.9 mg Zn/m^3, respectively. For exposure in the workplace categories 1-4, the values mentioned in **Table 4.2** will be taken forward to the risk characterisation.

The exposure is mainly to large particles (> 90% above 0.9 µm), with very small percentages in the range below 0.52 µm. The short-term exposure has been measured only a very few times and is therefore estimated to be twice the maximum measured exposure level: 8 mg Zn/m^3 (10 mg ZnO/m^3; expert judgement).

Dermal exposure

The tasks within the factories studied clearly lead to different exposure levels. Therefore, the exposure levels were clustered in levels for “high-” and “low-” exposure tasks. “High-exposure

tasks" are packing, classifying, blending and pelletising. "Low-exposure tasks" are furnace operation, warehouse operation and general operator. For both these clusters of tasks, dermal exposure levels will be concluded. Zinc oxide and zinc dust have different particle sizes and different dustiness. The results of the measurements however do not show clear differences between workers in zinc oxide and zinc dust sections of the plants A and B. Therefore, the assessment for dermal exposure in the production of both zinc oxide and zinc dust will be based on the combined results of zinc oxide and zinc dust workers. Six of the eleven "high-exposure group" workers in plants B and D have dermal exposure levels to zinc of hands and forearms between 1,750 and 2,250 mg zinc. A reasonable worst-case value for hands and forearms is therefore estimated as 2,000 mg zinc. Six of the ten "high-exposure group" workers (with full sets of samples) in plants B and D had whole body dermal exposure levels between 1,950 and 2,700 mg zinc. The highest value was found for a worker that had exceptionally high-exposure values for head/face and neck. Discarding this outlier, the highest five whole body dermal exposure values in the high-exposure group are between 1,950 and 2,400 mg zinc. A reasonable worst-case value of 2,200 mg zinc is therefore chosen for whole body exposure for the "high-exposure group". Typical exposure levels for the "high-exposure group" are estimated by values close to the GM of exposure levels for this group, i.e 1,200 mg zinc (hands and forearms) and 1,300 mg zinc (whole body, excluding the outlier with very high values for other body parts)

For the "low-exposure group", the reasonable worst-case dermal exposure level for hand and forearms is estimated as approximately 700 mg zinc, a value in the middle of the range of the highest 8 values (of 18 in total). The reasonable worst-case dermal whole body exposure level is similarly estimated as 850 mg zinc. Typical values are estimated as values close to the GM of exposure levels for this group, i.e. 350 mg zinc for hands and forearms and 450 mg zinc for the whole body.

It is assumed that activities of the high-exposure groups (packing, pelletising, blending) are of importance. The following conclusions are reached for dermal exposure in the production of zinc oxide:

- reasonable worst case: 2,740 mg zinc oxide; this is 2,200 mg zinc,
- typical case: 1,620 mg zinc oxide; this is 1,300 mg zinc.

The following uncertainties should be considered in the evaluation of the Margin of Safety (MOS). The fact that workers in the studied facilities partly used gloves (though generally intermittently) may have resulted in an unknown reduction of measured exposure levels and therefore underestimation of potential exposure. On the other hand, the dermal exposure is expected to slope to a maximum or ceiling at an unknown level. The measurement method (sampling three times per day) may have prevented this sloping effect and may have led to an overestimation of potential dermal exposure. This effect is expected to occur close to the maximum adherence of powder to the skin. According to a literature review, this maximum adherence is approximately 10 mg/cm^2 (SAIC, 1996). The calculated adherence of 2,740 mg zinc oxide on 2,000 cm^2 skin is with 1.4 mg/cm^2, far below this value. Therefore, this effect is expected not to be very important in this case.

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: Production of paint (and some other products) containing zinc oxide

Zinc oxide is used as a component in several applications, such as paint, rubber (including tyres), glass, ceramics, ferrites (< 5% ZnO), varistors, catalysts, feedstuff additives (up to 150 mg/kg), lubricant additives (generally < 1% ZnO) and cosmetics and pharmaceuticals (Industry, 1999b). The use of ZnO in paint is taken as an example of these uses with relatively high-expected exposure levels. The use of ZnO in rubber is described in the next scenario. The amount of ZnO in paints depends on the type of paint. According to the paint industry (ZOPA, 1998d) the content in anti-corrosive paint is generally 1-10%, in anti-fouling paint 5-45% and in other paints less. The exposure to zinc oxide mainly takes place when the compound is added as a solid. The duration of this activity is estimated to be at maximum 4 hours per day if several batches of paint containing ZnO are produced per day. The dustiness of ZnO is very low, compared to several other substances. In a study with one dustiness measuring method, the following amounts of dust were found for different substances: $CaCO_3$: 248-310 mg/100 g, TiO_2: 125-350 mg/100 g and 4.6-11.6 mg/100 g, Fe_2O_3: 19-31 mg/100 g and 32-59 mg/100 g and ZnO 1-5 mg/100 g (Heubach, 1991). The low dustiness value for one of the TiO_2 products is apparently reached by special treatment. The dustiness of zinc oxide has also been tested by a modified Heubach method. The total dustiness was found to be 30 mg/g with 84.53% larger than 8.13 μm and 73.92% larger than 15.8 μm (Deutsche Montan Technologie, 2000).

Measured data on zinc oxide

Measured data for zinc (oxide) or dust during the handling of zinc oxide in the manufacture of ceramics, ferrites and paint have been gathered by industry. Data from several industries are presented in **Table 4.5**.

Table 4.5 Exposure to Zn or dust in several industries during the use of ZnO (Industry, 1999b)

Industry	n	Duration	Exposure levels (mg/m³)*	References and remarks
Frits, enamels and ceramic pigments	212	n.g.	206 values < 0.8	
Ferrites	n.g.	n.g.	< 0.1	no details presented
Ferrites (specific company)	n.g.	n.g.	0.18-0.92	ZnO delivered in big bags exposure levels measured in several parts of the plant
Catalysts	n.g.	8-hours	0.1-2 0.5 (typical)	(at plant operations and bag unloading)
Catalysts (specific company)	108	180-510 min	0.001-6.13(GM) 6.8 (GSD)	90th percentile calculated from GM and GSD as 1.9 mg/m³.
Ceramics (one specific company)	n.g.	8-hours	1-7 (dust) with 10-14% ZnO	ZnO loaded from bulk transport to bulk storage
Feedstuff additives	n.g.	8-hours	< 5	no details presented

* Exposure levels generally expressed as amount of Zn/m³.

Data provided by the paint industry are presented in **Table 4.6**.

Table 4.6 Exposure to total dust in the production of paint (CEPE, 1998)

Set	Situation	n	Duration of sampling (min)	Results (mg/m^3)	Exposure calculated over 8 hours(mg/m^3)
A	emptying ZnO form big bags into dispensers	3	22-33	2.6-4.9	0.17-0.28
B	loading powders from 25 kg bags into dispensers	19	< 30	n.g.	0.01-1.5, average 0.29
C	loading powders from big bags into dispensers	12	< 30	n.g.	0.01-1.34, average 0.27
D	bag disposal	n.g.	n.g.	average 1.04 maximum 2.2	n.g.

n.g. = not given

These results are for total dust. The ZnO content in the dust is unknown.

Measured data on other compounds

In a recent study on the exposure to inhalable dust during loading of powders into mixers in 10 different facilities both exposures during loading and full-shift exposure was measured (Marquart et al., 1999a). All mixers were equipped with LEV that was observed to function properly in all but one situation. A variety of powders were loaded (not including ZnO), generally from 25 kg bags, but in some cases also from big bags or drums. Exposure levels of inhalable dust averaged over all loading tasks of one worker ranged from 1.9 to 27.6 mg/m^3. Duration of total loading tasks varied from 20 to 222 minutes and the amount of powder loaded by one worker during the shift from 330 to 11,369 kg. Full-shift exposure levels to inhalable dust measured ranged from 0.8 to 12.1 mg/m^3. Measurements related to ZnO from other industries where ZnO is mixed into products (e.g. rubber, ceramics, surfactants) are reported as medians over 8 hours of < 0.1-1.5 mg/m^3 and ranges over up to 8 hours of < 0.2-6 mg/m^3. Short-term exposure levels in one facility during loading were 2.5-5 mg/m^3 (ZOPA, 1998e). For bag filling and bag dumping "reasonable worst-case" estimates in the presence of LEV with limited effectiveness were deduced from literature of 1.8 and 10 mg/m^3 (respirable and total dust concentrations during bag filling) and 10 mg/m^3 (total dust concentration during bag dumping (Lansink et al., 1996a).

From measured data on calcium carbonate in the paint industry (Lansink et al., 1996b) exposure levels of the hands during different activities were derived, using cotton glove samplers of approximately 1,600 cm^2. The mean (GM) for collecting raw material was 476 mg/day (range 139-1,090, n = 12), for manual weighing the GM was 685 mg/day (range 247-2,511, n = 6), for manual dumping the GM was 888 mg/day (range 123-4,214, n = 19) and during collecting empty bags the GM was 215 mg/day (range 53-1,042, n = 14). The 90th percentile for manual dumping was 3,000 mg/day.

The data from Hughson and Cherrie (2001) on dermal exposure levels in the production of ZnO are at least partially relevant, specifically for unloading of intermediate bulk containers or big bags, which was part of the tasks of some workers (see Scenario 1).

Models

Inhalation exposure to dust during production of paint containing zinc oxide is estimated with the EASE model as 2-5 mg/m^3 assuming aerosol formation during dry manipulation and presence of LEV.

Dermal exposure for dry manipulation of the substance (wide-dispersive use and intermittent contact) was estimated as 1-5 mg/cm^2/day. When the palms of both hands are exposed (surface area 420 cm^2) dermal exposure is estimated to be 420-2,100 mg/day.

Conclusions

Inhalation exposure

The data presented by various users of zinc oxide are rather variable in detail. Part of the data appears to relate to "typical exposures" and for those data it is unclear what the variation in exposure levels is. Some of the data relate to the use of ZnO from bulk transport containers, other data relate to ZnO used from big bags and some data probably relate to use of ZnO from bags. The data from the paint industry appear to relate to one facility producing anti-fouling paints and are partly related to ZnO and partly to powders in general. In general, undetailed information is presented by industry sectors, while detailed information is available from single companies. Where detailed data are available, they are not all fully consistent with the summarised industry sector data. It is therefore very difficult to assess the representativeness of the data for the full industry sectors.

The data from Marquart et al. (1999a) in the paint, adhesives and pharmaceutical industry are representative for manual dumping of powders from bags in mixers fitted with LEV. They were all measured for other substances than zinc oxide and included both coarse granular substances and fine powders, often within one measurement. This study shows that there is remarkable variation in exposure levels, probably partly due to differences in powders handled and partly to differences in working method and effectivity of the LEV. The study also shows, that exposure is not negligible during other activities than loading (e.g. manual weighing and other handling of powders). Based on the literature survey by Lansink et al. (1996a) and the study by Marquart et al. (1999a) it can be concluded that exposure levels can be as high as 20 mg/m^3 during manual handling of large amounts of (dusty) powders. Dust exposure levels can be up to 10 mg/m^3 for an 8-hour shift. Zinc oxide has a very low dustiness compared with some other tested substances, such as calcium carbonate. The model EASE presents 2-5 mg/m^3 as the exposure level for manual handling of powders with LEV. It is expected that the data presented by Marquart et al. (1999a) overestimate the exposure to ZnO, because they include substantially dustier solids. The same is to be expected from the literature data compiled by Lansink et al. (1996a). The results presented by the paint industry shows that dust exposure levels during actual dumping can be up to 5 mg/m^3. This value agrees with the estimate by EASE. Other industries mention exposure levels of up to 2 and 6 mg Zn/m^3 over 8 hours. Combining all this information it is concluded that reasonable worst-case exposure levels due to loading of zinc oxide from (big) bags may be up to 5 mg ZnO/m^3, for a maximum duration of 4 hours. The reasonable worst-case full-shift exposure level is estimated to be up to 2.5 mg ZnO/m^3. Short-term exposure levels (e.g. 15 minutes) are expected to be up to 10 mg ZnO/m^3. For a typical value for inhalation exposure a value of 0.5 mg ZnO/m^3 is used, taken from the measured values mentioned by industry for ZnO.

Dermal exposure

Two sets of data are available for situations that are somehow analogous to the situation to be assessed. The data by Hughson and Cherrie (2001) are for the substance itself, but for a process that is different from the assessed process. The data on calcium carbonate from Lansink et al. (1996b) are for another substance, but for the process to be assessed. A difference between the studies is, that the data from Hughson and Cherrie are for a full shift, while the data from Lansink et al. are for one batch of paint. The data on calcium carbonate could therefore underestimate full-shift exposure levels. It is not known how many batches of paint are made per day using zinc oxide, but a number of batches above two are not expected. On the other hand, calcium carbonate is much more dusty than zinc oxide and this may lead to overestimation of exposure to zinc oxide by the calcium carbonate data. A comparison of dermal exposure in the production of zinc oxide and zinc dust (that is of substantially lower dustiness than zinc oxide) does not show clear differences due to dustiness. The measurement method of Lansink et al. (1996b) – cotton gloves - may have led to an overestimation of the true exposure levels because powder may adhere better to cotton than to bare skin. A comparison on the basis of the measured values shows that the estimates of reasonable worst case based on Hughson and Cherrie (2001) and Lansink et al. (1996b) are comparable: 2,740 mg zinc oxide for high-exposure tasks in the production of zinc oxide or zinc dust and 3,000 mg calcium carbonate for dumping into mixers. The typical value is lower for dumping of calcium carbonate: 900 mg versus 1,300 mg for high-exposure tasks in the production of zinc oxide or zinc dust. No information is available to show what possible bias in measurement method, process, and number of batches or substance characteristics is more influential. Therefore, the more conservative of the two available analogous 90^{th} percentiles are taken forward to the risk characterisation: 3,000 mg zinc oxide/day (i.e. 2,400 mg zinc/day). Similarly, the more conservative of the two available typical values are taken forward to the risk characterisation: 1,620 mg zinc oxide/day (i.e. 1,300 mg zinc/day).

The uncertainties that should be considered in the evaluation of the MOS are largely mentioned above. Although the repeated sampling by wet wipes may also overestimate exposure levels (due to the prevention of a possible "sloping effect"), this is not likely to be very important in this case, since the total level of contamination per cm^2 is still clearly below values that were considered to represent the maximum adherence of powders to the skin by SAIC (1996). The value of 3,000 mg is 1.5 mg/cm^2 for a 2,000 cm^2 surface area, while SAIC concludes that the maximum adherence of powders is approximately 10 mg/cm^2, based on literature studies. The process of dumping powders from bags is considered to lead to higher dermal exposure than the filling of bags, due to the higher powder/air interaction in dumping and possible direct contact of the flow of powder with the skin. The reasonable worst-case and typical values may therefore be under estimated by the values taken forward to risk characterisation.

The duration of exposure during actual handling of ZnO is estimated to be up to 4 hours per day, with a frequency of up to 200 days per year.

4.1.1.2.3 Scenario 3: Use of zinc oxide in the rubber industry

Zinc oxide is added in the rubber industry in small amounts (up to a few kilos at a time), several times per day. In approximately half of the facilities the adding and mixing of components is highly automated, but in the other facilities more manual adding with intermittent contact occurs. A typical work step, such as the weighing of a few kilos of ZnO or the dumping of that amount into a pre-mixer takes only up to 30 seconds (Industry, 1999c).

Measured data on zinc oxide and other compounds

Data from 27 plants in the tyre industry were compiled to a so-called "median plant". Exposure of workers is mentioned to be up to 50% of the working time and exposure levels of ZnO are reported to be 0.5 mg/m^3. A "median plant" has also been constructed from 14 plants that have answered questions for the general rubber industry. Exposure is reported for up to 30% of working time with total dust levels of 5.9 mg/m^3 and ZnO concentration of 1.5 mg/m^3 (ZOPA, 1998e). An industry description of use of ZnO in the tyre industry reports that exposure levels to total dust are below 5 mg/m^3 and are typically 2-3 mg/m^3 (Industry, 1999c).

The German BAuA measured exposure levels of total dust in a number of rubber product companies (Rentel et al., 1991). Exposure levels were particularly high for weighing of substances, that was done mostly manually, but dust levels were also high for filling of the mixer (mostly automatically). Generally the weighing sites were equipped with LEV. Exposure to total dust was generally very high:

- weighing: 0.85-74 mg/m^3 (n = 11), with a 90th percentile of 41 mg/m^{3,}
- filling: 0.98-18.5 mg/m^3 (n = 7), with the second highest value being 16 mg/m^3.

Kromhout et al. (1994) report measurements of airborne particulates in 10 rubber product companies. The geometric mean for compounding (over all samples) was 2 mg/m^3 inspirable dust, with a GSD of 3.4 (n = 99). From these data a 90th percentile of 9.6 mg/m^3 can be calculated. The GM for weighing (as a part of compounding) was 3.5 mg/m^3, with a 95% confidence interval of 2.5-5.1 mg/m^3. The HSE-UK (2000) reported four measured values of 0.001 mg/m^3 in rubber moulding. Dost et al. (2000) collected exposure data from 88 rubber companies with 361 personal (8-hour TWA) dust exposure samples. Exposure data (n = 104) were gathered for total dust in weighing, mixing and milling operations (known to cause the highest dust exposures). Data were classified in the general rubber goods and new tyre companies.

Company type	Samples (N)	Mean	Median	Minimum	Maximum
General rubber goods	82	2.3	1.0	0.02	18.6
New tyre companies	22	2.2	1.6	0.1	9.64

From these data, the 90th percentile for total exposure to dust is 6.0 mg/m^3. The calculated reasonable worst-case inhalation exposure to ZnO is 0.38 mg/m^3 ((6 mg/m^3 · 1.5/5.9 (ZnO fraction) · 2/8 (job duration)).

There are no measured data for dermal exposure to zinc oxide in the rubber industry. Kromhout et al. (1994) measured skin exposure to cyclohexane soluble matter (CSM). However, this refers to organic compounds that are used differently and lead to a different dermal exposure situation than ZnO. Exposure to inhalable particles and dermal exposure to CSM was evaluated in 1988 and in 1997 to study the effectiveness of control measures (Vermeulen et al., 2001). A reduction rate was measured of 5.7% per year for inhalable particulate and 6.7% per year for dermal exposure. Companies and production functions with the highest exposure levels in 1988 showed a steeper decline in exposure levels. Reduction of emission did not show a significant overall decrease in exposure concentrations.

The data by Lansink et al. (1996b) on $CaCO_3$ in the paint industry may partially be relevant. The most relevant data are those for manual weighing, where the GM was 685 mg/day (range 247-2,511, n = 6). The weighing generally had a duration of 2-5 minutes during which 3-38 kg was weighed. The measurements by Hughson and Cherrie (2000) in zinc oxide production are also partly relevant.

Models

Inhalation exposure to dust during production of paint containing zinc oxide is estimated with the EASE model as 2-5 mg/m^3 assuming aerosol formation during dry manipulation and presence of LEV.

Dermal exposure for dry manipulation of the substance (wide-dispersive use, LEV present and intermittent contact) was estimated as 1-5 mg/cm^2/day. When the palms of both hands are exposed (surface area 420 cm^2) dermal exposure is estimated to be 420-2,100 mg/day.

Conclusions

Inhalation exposure

Inhalation exposure due to handling of ZnO in rubber product production is expected to be limited to the weighing and filling of the compounders. Total dust levels in rubber companies can be very high. The tyre production is highly automated including automated weighing, leading to relatively low-exposure levels. However, small-scale batchwise production of specialty products needs more manual weighing and filling and probably leads to substantial inhalation and dermal exposure to dust. Since ZnO is only a small part of the total product, is handled in small amounts at a time and is not very dusty, measured exposure levels of total dust are expected to be substantially higher than the levels of ZnO. Industry mentions a total dust level for the manual handling of up to 5.9 mg/m^3, with a ZnO exposure level of 1.5 mg/m^3. The data are limited in detail. It is expected that these values are more or less typical values. Compared to the data by Rentel et al. (1991) and the large data set by Kromhout et al. (1994) the value of 5.9 mg/m^3 total dust as presented by industry is rather low. The data presented by Dost et al. (2000) are comparable with those of Kromhout et al. (1994). The lower 90^{th} percentile of the data presumably reflects the tendency in the rubber industry that reduction of exposure is being achieved by control measures. The calculated 90^{th} percentile of the data by Dost (6 mg total dust/m^3) will be used as a basis for the estimator of the reasonable worst case in situations where relatively large amounts of ZnO are handled manually. During this period, the duration of handling ZnO is limited and is estimated to be up to 2 hours/day. If the same ratio total dust/ZnO is used as in the data presented by industry, the reasonable worst-case exposure level to ZnO during the period of handling is approximately 1.5 mg/m^3 ($6 \cdot 1.5/5.9$). The 8-hour time weighted average is calculated to be up to 0.4 mg/m^3 ($1.5 \cdot 2/8$). Peak exposures up to 5 mg ZnO/m^3 are expected to occur. A typical full-shift exposure level is expected to be 0.1 mg/m^3 (expert judgement).

Dermal exposure

Specific dermal exposure data for ZnO in the rubber industry are not available. The processes can be compared to those in the paint industry. However, the amounts handled are generally substantially less, leading to lower exposure levels. It is expected that the exposure levels for rubber product producers who (within their sector) handle relatively large amounts of ZnO can be compared to the dermal exposure in the production of ZnO.

It is assumed that activities of the high-exposure groups (packing, pelletising, blending) are of importance. The following conclusions are reached for dermal exposure in the production of zinc oxide:

- reasonable worst case: 2,740 mg zinc oxide; this is 2,200 mg zinc,
- typical case: 1,620 mg zinc oxide; this is 1,300 mg zinc.

The following uncertainties should be considered in the evaluation of the MOS. The data gathered by Dost et al. (2000) are mainly based on measurements in companies in the northwestern part of Europe. These companies in general are active in reducing exposure with reduction measures. This is reflected in the lower measured values in the near past compared with several years ago. This database may therefore not be representative for Europe as a whole. The fact that workers in the studied facilities partly used gloves (though generally intermittently) may have resulted in an unknown reduction of measured exposure levels and therefore underestimation of potential exposure. On the other hand, the dermal exposure is expected to slope to a maximum or ceiling at an unknown level. The measurement method (sampling three times per day) may have prevented this sloping effect and may have led to an overestimation of potential dermal exposure. This effect is expected to occur close to the maximum adherence of powder to the skin. According to a literature review, this maximum adherence is approximately 10 mg/cm^2 (SAIC, 1996). The calculated adherence of 2,740 mg zinc oxide on 2,000 cm^2 skin is with 1.4 mg/cm^2, far below this value. Therefore, this effect is expected not to be very important in this case.

4.1.1.2.4 Scenario 4: Use of paints containing zinc oxide

ZnO is mainly used in anti-corrosive paints (with a pigment portion generally 1-10%, up to 35%) or antifouling paints (pigment portion generally 5-45%, up to 60%), generally in the outdoor environment, although some use in wall paint (up to 3%) is also possible (CEPE, 1998). Zinc oxide will seldom be more than 50% of the pigment. Assuming a typical concentration of 25%, the zinc oxide content will be up to 12.5%. Paints for spraying operations will require further dilution. A typical value of 5% zinc oxide is assumed. The worst-case exposure to zinc oxide, using zinc-containing products is represented by the use of paint applied as a spray.

Measured data on zinc oxide

The UK HSE (2000) database mentions an exposure to ZnO during spray-painting ranging from 0.5-1.3 mg/m^3, with an average of 0.4 mg/m^3 (n = 9). No further details, such as a job description, are mentioned.

Measured data on other compounds

An alternative approach is used based on exposure to other substances (De Pater and Marquart, 1999). Several literature sources have been studied regarding exposure levels for solid substances (or very low vapour pressure liquids) during spray-painting, including 13 references on polyisocyanates and 10 on “total dust”. Exposure variability is very high, probably due to differences in spray-painting techniques, percentages of the measured compounds in the paint and control measures. However, the influence of these parameters cannot be derived from the literature data. From these sources two general approaches have been derived for estimation of exposure levels.

1) $E_s = 50 \cdot f_s/75$

where: E_s = the estimated exposure level for the notified substance;
50 = the estimated reasonable worst-case exposure level "total dust";
f_s = the fraction of notified substance in total solids of the paint;
75 = the reasonable worst-case percentage of "total solids" in paints.

General assumptions in this approach are:

- measured "total dust" consists of only non-volatile compounds,
- the same linear relation exists between the percentage of substance in paint and the percentage of substance in paint mist for total dust and for the substance assessed.

A further assumption regarding the percentage of total solids in the specific paint may be necessary.

2) $E_s = 10 \cdot f_s/30$

where: E_s = the estimated exposure level for the notified substance;
f_s = the percentage of the notified substance in total paint;
30 = the percentage of polyisocyanates in total paint;
10 = the estimated reasonable worst-case exposure level for polyisocyanates.

General assumptions in this approach are:

- both the notified substance and the polyisocyanates are non-volatile.
- the same linear relation exists between the percentage of substance in paint and the percentage of substance in paint mist for polyisocyanates and for the substance assessed.

A comparison by cross-referencing of both approaches shows more or less similar results. Due to the somewhat better overall quality of the data set for polyisocyanates, the approach based on measurements for these compounds was considered to be most reliable.

An equation for a typical combination of percentage of polyisocyanates and typical exposure levels was derived from the same data and was $E_s = 1 \cdot f_s/10$.

Calculations for this substance

The percentage of zinc oxide paints is assumed to be up to 12.5% (reasonable worst case for anti-fouling paints). In other paints, a typical value of 5% is assumed. The reasonable worst-case exposure level for ZnO during spray-painting is calculated as $E_s = 10 \cdot 12.5/30 = 4.0$ mg/m^3. The typical exposure level is calculated as $E_s = 1 \cdot 5/10 = 0.5$ mg/m^3.

For dermal exposure the results of measurements done for spray coating of containers with anti-corrosive paints can be used in the analogy approach. Lansink et al. (1998) measured potential dermal exposure levels of professional painters in the offshore industry, using the airless spray-painting technique to paint a container. The outside of a container was painted in total 21 times and the inside only 5 times. Twelve painters participated. The paint was specially mixed to contain no pigment, but a small percentage of fluorescent tracer. The amount of tracer on the skin and coverall was determined after spraying using a fluorescent imaging and data analysis system. After approximately 10 minutes of spraying, a 90th percentile of 22 µg of tracer was found on hands and face. Linearly extrapolating from the percentage of tracer (0.0074%) and the duration of painting (10 minutes) up to the full substance (100%) and 3 hours of

painting, the total potential exposure to paint after 3 hours is estimated to be 5,350 mg for hands and face. With a surface area of approximately 1,300 cm^2, this is approximately 4.1 mg/cm^2/day (Marquart et al., 1999b). Using these measurements to conclude on the exposure to zinc oxide (12.5% in paint), the estimated reasonable worst-case exposure to zinc oxide in paint spraying is $0.125 \cdot 4.1 = 0.5$ $mg/cm^2/day \cdot 1{,}300$ cm^2 is approximately 670 mg/day.

Models

Spraying of paint may lead to inhalation and dermal exposure. EASE is however considered unsuitable for estimating inhalation exposure due to spray coating. The option of "aerosol formation" in the estimation of exposure to liquids is aimed at accounting for the increased evaporation due to fine dispersion of liquids in the air. The spraying of paint is also clearly not "dry manipulation of solids" and can hardly be considered a "low dust technique".

The dermal exposure is estimated as extensive contact, wide-dispersive use and direct handling of the substance. With an exposed surface of 1,300 cm^2 (both hands and part of the forearms) and an estimated exposure of 5-15 mg/cm^2/day the result is 6,500-19,500 mg/day. With a reasonable worst case of 12.5% zinc oxide of the paint, exposure is up to 2,440 ($15 \cdot 1{,}300 \cdot 0.125$) mg/day.

Conclusions

Inhalation exposure

For the worst-case use of products containing zinc oxide (spraying of paints) the calculations on the basis of the analogy will be used for inhalation exposure. The EASE model in this case overestimates exposure and only a few measured data are available, lacking a proper job description and details on the percentage of zinc oxide in the paint used. The calculated value of 4 mg/m^3 is taken as a reasonable worst-case value for inhalation exposure during up to 4 hours with a short-term exposure of twice this value (8 mg/m^3). The full-shift exposure is calculated to be up to 2 mg/m^3, assuming negligible exposure outside of the period of spray-painting. This value is higher than the average of the few measured values, but close to the highest value of this small set of data.

Dermal exposure

Dermal exposure is estimated to be 670 mg/day, based on the analogy approach. EASE is expected to overestimate the exposure levels and specific data on zinc oxide are not available. The use of PPE (coveralls, gloves and respirators) is common in the spraying of paint. However, it is known that PPE is not always worn consistently. In a study by Preller et al. (1998) RPE was not worn during 9% of the total spray-painting time of 25 workers (no details presented on distribution over workers). In 5 car body repair shops workers did not wear RPE or gloves during 3-38% of the spray-painting activities (De Pater et al., 1998). A proper regime of storage, replacement and maintenance of PPE is necessary for a proper effect of PPE. Such a regime is not expected to be in place in many spray-painting facilities. Therefore, the use of PPE is not accounted for in the exposure assessment.

The following uncertainties should be considered in the evaluation of the MOS. The fact that workers in the studied facilities partly used gloves (though generally intermittently) may have resulted in an unknown reduction of measured exposure levels and therefore underestimation of potential exposure. On the other hand, the dermal exposure is expected to slope to a maximum or

ceiling at an unknown level. The measurement method (sampling three times per day) may have prevented this sloping effect and may have led to an overestimation of potential dermal exposure.

The total duration of exposure is estimated to be more than 4 hours per day (4 to 6 hours per day), with a frequency of up to 200 days per year. However, since exposure to the reasonable worst-case exposure level is not expected during the maximum exposure duration, the full-shift exposure level is calculated based on 4 hours

4.1.1.2.5 Scenario 5: Zinc die casting

The feedstock for die casting is high purity zinc alloy ingot made to stringent chemical composition standards. The melting is usually done in a bulk melting furnace. Temperatures are kept at 400-450°C. Clean foundry returns may be added to the virgin ingot. Precise temperature control is used in order to maintain the metallurgical quality of the metal. Molten metal is taken from the bulk melter to the die casting machines by a variety of mobile ladle systems or by a launder (data from HEDSETs, IUCLID, 1996).

The holding furnace is an integral part of the die casting machine. Casting is by direct injection into steel moulds. The die faces are merely protected by applying small quantities of wax based parting agents. Once the casting is solid the die opens, the casting is ejected and the cycle is repeated. Very thin holes are used to connect the running system to the cast component. The runners etc. are usually returned to the melting furnace for direct recycling. Exposure to aerosols formed by emission of fumes (condensed volatilised zinc) is possible. Direct unprotected handling of zinc compounds does not occur, due to the fact that material handled is hot. However, dermal exposure due to contamination of equipment and surfaces, after cooling of material is possible.

Measured data on zinc compounds

Data are provided by the HSE-UK (2000) and several companies (see Table A1, Appendix A). The UK HSE (2000) reported a range of concentrations from 0.02 to 2.71 mg/m^3 (n = 12, AM = 0.6 mg/m^3). The reported values of several companies were from personal as well as static sampling. Measurements were done during a complete day shift under normal production conditions. Some of the static sampling was done with sampling heads for personal monitoring. The results are expressed as particulate levels (mg/m^3). Analysis of the particulates shows a typical zinc content of 10 to 20%. The concentration of zinc compounds expressed as 'zinc' ranged from 0.015-1.0 mg/m^3 with a typical value of 0.1 mg/m^3. Due to the process, where molten zinc is in contact with oxygen in the air, the exposure is expected to be mainly to zinc oxide.

No measured data on dermal exposure to zinc compounds are available for this scenario. It is expected that the dermal exposure data for galvanising are also representative of the situation regarding dermal exposure in die casting. 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 4.7**.

Table 4.7 Results of the measurement of zinc exposure levels (mg zinc) 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 (1,64.8 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).

Measured data on other substances

No measured data on other relevant substances for this specific scenario are available. However, measured data by Wheeler et al. (1999a;b) on dermal exposure to lead in the battery industry (and partly in other industries) may be relevant, since the exposure route (mainly indirect exposure via contaminated surfaces) and the use of PPE (common for possibly exposed workers) is similar. The exposure was measured by hand washing, with a recovery that was estimated from laboratory experiments to be 85%. The measured exposure levels in the first study for workers with subjectively assessed relatively high exposure were between 0.5 and 178.6 µg/cm^2. Almost all workers with a ranking 2 or 3 wore gloves during work, although the worker with the highest measured level did not wear gloves (Wheeler et al., 1999c). The maximum adherence to hands (actual exposure) in the second study was 104 µg/cm^2 and a 90th percentile of approximately 50 µg/cm^2 can be deduced from the presented graphs. Approximately half of the workers wore gloves (Wheeler et al., 1999c).

Models

An estimation of possible inhalation exposure to zinc aerosols can be made using the EASE model with the following assumptions (TGD, 1996). Most handling of zinc occurs at temperatures just above the melting point (415-420°C). The vapour pressure of zinc in that situation is ca.

15 Pa. Assuming a process temperature of 420°C, non-dispersive use and presence of local exhaust ventilation (LEV), an exposure level of 0.5-1.0 ppm (1.4-2.8 mg/m^3) is estimated using EASE version 2 for Windows. This version is preferred due to the better discrimination according to vapour pressure.

For dermal exposure it is assumed that contact with contaminated material is possible, which is assessed by assuming non-dispersive use, incidental contact and an exposed surface area of 420 cm^2 (half of two hands). This leads to an estimate of 0-0.1 mg/cm^2/day $\cdot$ 420 cm^2 = 42 mg/day. This is expected to be exposure mainly to zinc oxide.

Conclusions

Inhalation exposure

There are measured data for inhalation exposure from several sources. The reports are not very detailed regarding exposure determinants and measurements and in some cases it is unclear whether the process was indeed zinc die casting or brass casting. Nevertheless, the measured data are considered representative for Europe. They are therefore used for risk characterisation, with a typical value for inhalation exposure of 0.1 mg/m^3. A value of 1 mg/m^3 is estimated as a reasonable worst case for this scenario, and a short-term value of twice this value is used: 2 mg/m^3. The reasonable worst-case value is the highest level measured in Company U (1996), which is clearly below the very high value of 17 mg zinc/m^3 reported by HSE (2000), but not far from the range measured by Company G (1996).

The following uncertainties should be considered in the evaluation of the MOS for this scenario. The presentation of data was so limited, that it was difficult to conclude whether data were indeed for this process or for brass casting and how many data points were actually available. This leads to a relatively large uncertainty in the assessment. If the data that are used for this scenario are mainly for brass casting (as industry suggested), the exposure estimate is probably an overestimate for zinc die casting, as brass casting appears to lead to higher concentrations. The uncertainty is further enlarged by the fact that the data are a mixture of static and personal sampling. No data is available that indicates whether or not the static samples can really be considered representative for personal exposure.

Dermal exposure

In this scenario direct manual contact with hot materials is not expected. However, dermal exposure due to contact with contaminated surfaces is possible. The exposure levels as measured by Hughson and Cherrie (1999; 2000) and by Wheeler et al. (1999b;c) are considered relevant, since in the measured situations workers were also mainly exposed indirectly via contaminated surfaces. 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. The estimate for full-shift dermal exposure will be based on the approximate 90th percentile of the data of the galvanising facilities in the second survey, because in that survey a better sampling method was used. This value is 140 mg zinc/day for the whole body. The value for whole body recalculates in 175 mg zinc oxide/day. The typical value for the whole body is taken from the middle of the measured range (approximate median) and is 70 mg zinc/day. The typical whole body value recalculates in approximately 85 mg/day.

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 underestimation of the reasonable worst case for less well-equipped facilities.

The duration of inhalation exposure is assumed to be up to 8 hours per day. Exposure frequency is estimated to be up to 200 working days (expert judgement).

4.1.1.2.6 Scenario 6: Brass casting

Brass casting involves the melting of brass (alloy of copper and zinc, usually in a proportion of 2:1) in a large furnace before being transferred to crucibles from which it is poured into casts. Temperatures of the product are in excess of 900°C. As zinc boils at a lower temperature than copper, considerable quantities of zinc containing aerosols are generated. The highest amounts are produced during transfer and pouring of the metal and when the furnaces are cleaned (Groat et al., 1999).

Measured data on zinc compounds

Several data sets are reported that apparently are related to brass casting. Industry (1996) reported dust exposure data from three foundries involved in zinc alloy die casting. An unknown number of data showed values of 0.1-3.3 mg/m^3. Company AD (1999) reported data from a batchwise process before 1998 with exposure of 3-5 mg zinc/m^3 and from a continuous process after 1998 with exposures below 0.1 mg zinc/m^3. Measurements by Groat et al. (1999) in a brass-casting facility can be used to indicate exposure levels and particle size distributions in this process. The measurements were done to study the particle size distribution. However, total inhalable dust exposures were also calculated. Since the zinc die casting process is run at a lower temperature than brass-casting, exposure to zinc oxide for this industry may be considered as exposure to an analogous substance. Two sites were studied, with four furnace operators each. Exposure levels in the first site were reasonably comparable for all workers: 0.1-1.8 mg zinc/m^3 (recalculated into 0.1-2.2 mg ZnO/m^3), while there were substantially higher exposure levels in the second site: 2.5-16.8 mg zinc/m^3 (recalculated into 3.1-20.9 mg ZnO/m^3). The sample volumes in site 2 were approximately half those in site one, indicating that the duration of sampling was substantially less than full shift. The particle size distribution were as follows: site 1: 28-41% > 21.3 μm; 74-82% > 3.5 μm; 2-10% < 0.52 μm; site 2: 33-60% > 21.3 μm; 70-90% > 3.5 μm; 1-8% < 0.52 μm. The exposure levels for aerosols < 0.52 μm can be calculated to be up to 0.32 mg/m^3 (expressed as zinc). Particle sizes were also studied by Harrison et al. (1981) and O'Neill et al. (1982) in primary zinc-lead smelters. Generally, only less than 10% of the exposure to Zinc was in particles < 0.5 μm. By EBRC (2001f) data were collected from 8 major brass companies and evaluated in a database. Data can be divided in inhalable, respirable and (calculated) ultra fine particles. With n = 28, the median for the inhalable fraction was 0.4 mg Zn/m^3 and the 90th percentile 1.6 mg Zn/m^3. With n = 22, the median for the respirable fraction was 0.16 mg Zn/m^3 and the 90th percentile was 0.9 mg Zn/m^3. Combining these databases and assuming that 10% of the inhalable particles and 20% of the respirable particles are ultra fine, the median of ultra fine particles is 0.035 mg Zn/m^3 and the 90th percentile is 0.16 mg Zn/m^3.

Conclusions

Inhalation exposure

There are several sets of measured data for inhalation exposure. The data submitted by EBRC (2001f) are considered to be representative for Europe and will be used in the risk characterisation. As a reasonable worst case, the 90th percentile of the inhalable particles will be used 1.6 mg Zn/m^3, as a typical value, the median of the same distribution will be used 0.4 mg/m^3. As a short-term value, twice the RWC will be used: 3.2 mg/m^3.

The exposure is considered to be exposure to the zinc oxide aerosol, with a particle size distribution with 28-60% of particles > 21.3 μm and only 1-10% of particles < 0.52 μm. The reasonable worst-case short-term exposure to these very fine particles, assuming 10% of the inhalable fraction and 20% of the respirable fraction are ultra fine, is calculated to be up to 0.16 mg/m^3

Dermal exposure

In this scenario, like in the scenario for die-casting, direct manual contact with hot materials is not expected. However, dermal exposure due to contact with contaminated surfaces is possible. The exposure levels as measured by Hughson and Cherrie (1999; 2000) and by Wheeler et al. (1999b;c) are considered relevant, since in the measured situations workers were also mainly exposed indirectly via contaminated surfaces. 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. The estimate for full-shift dermal exposure will be based on the approximate 90th percentile of the data of the galvanising facilities in the second survey, because in that survey a better sampling method was used. This value is 140 mg zinc/day for the whole body. The value for whole body recalculates in 175 mg zinc oxide/day. The typical value for the whole body is taken from the middle of the measured range (approximate median) and is 70 mg zinc/day. The typical whole body value recalculates in approximately 85 mg/day.

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 underestimation of the reasonable worst case for less well-equipped facilities.

The duration of inhalation exposure is assumed to be up to 8 hours per day. Exposure frequency is estimated to be up to 200 working days (expert judgement).

4.1.1.2.7 Scenario 7: Exposure to zinc oxide during welding

Exposure to zinc oxide during welding by means of inhalation is in the form of metal fumes. Because of the high temperatures of the welding torch a “flash evaporation” of the metal is possible, yielding possible high concentrations of zinc fumes, that are transformed to zinc oxide. Welding fumes are known to consist of a large percentage of very small particles. Specific data on particle size for the measured data below are not available. The fumes are usually measured as dust (“total” or “respiratory”) and the zinc content of these fumes is usually expressed as elementary zinc or zinc oxide.

During batchwise welding after galvanising of steel products with hand held arc welding equipment, vaporisation of the zinc coating can occur, which will lead to the formation of zinc oxide. This problem is often avoided by removing the zinc coating in the vicinity of the weld. Continuous welding is done with thin sheets of zinc coated steel, which are used in large quantities in the auto industry. These processes are carried out by robots, also in other industries. The only possibility of exposure is during human intervention in the process.

Measured data

The process of welding and cutting of steel is a well-researched process. Most of the exposure data are collected during the use of rustproof steel and concern exposure to fumes, nickel etc. Data for the exposure to zinc (oxide) are scarce. Only if the steel is covered with a zinc containing coating, such as zinc chromate primers, exposure to zinc is expected. One study (Wal, 1990) reported full-shift exposure levels ranging from 0.1 to 0.8 mg/m^3. In another study (Marquart et al., 1989) exposure during welding of zinc coated materials showed full-shift exposure levels of zinc averaging 0.03 mg/m^3. The HSE database (HSE, 2000) mentions a range of 0.07-0.2 mg ZnO/m^3 (n = 4) and 0.01-0.52 mg Zn/m^3 (n = 19) during welding in general engineering. HSL (2001) collected 95 samples on 12 sites of which approximately 80 were from stainless steel welding. The welding fume concentrations of the majority of samples, taken behind welding face shields were well below 5 mg/m^3. Some very high results were obtained for welders wearing samplers on the lapels, outside the respirators. In 23 of the samples Zn was analysed. The average concentration was 0.05 mg/m^3.

Conclusions

Inhalation exposure

The (few) measured data are taken as reference with a typical value for exposure of 0.1 mg/m^3 and a worst-case value of 0.8 mg/m^3. A short-term exposure level is estimated to be twice the reasonable worst-case exposure 1.6 mg/m^3. The exposure estimates are rather uncertain, due to their small numbers and the fact that they are generally rather old. The welding process and the ventilation used in modern facilities may lead to lower levels.

Dermal exposure

Dermal exposure is estimated to be negligible.

Table 4.8 Conclusions of the occupational exposure assessment

Scenario	Activity	Frequency (days/year)	Duration (hours/day)	Inhalation exposure				Skin exposure	
				Reasonable worst case (mg ZnO/m³) ‡	Method	Typical exposure (mg ZnO/m³) ‡	Method	Reasonable worst case	Typical
1. Production of zinc oxide [a)]	full shift production recycling workplace 1 workplace 2 workplace 3 workplace 4 short term	100-200 100-200	6-8 0.25	 4.8 (3.9) 4.8 (3.9) 2.1 (1.7) 2.0 (1.6) 2.0 (1.6) 5.3 (4.3) 10 (8)	 measured expert	 0.85 (1.1) 0.9 (1.1) 0.4 (0.5) 0.6 (0.7) 0.6 (0.7) 0.8 (1.0)	 measured	2,740 (2,200)*	1,620 (1,300)
2. Production of paints containing zinc oxide [a)]	dumping full shift short term	100-200 100-200 100-200	2-4 6-8 0.25	5 (4) 2.5 (2) 10 (8)	analogy measured / analogy analogy	0.5 (0.4)	measured	3,000 (2,400) **	1,620 (1,300)
3. Production of rubber products containing zinc oxide [a)]	dumping full shift short term	100-200 100-200 100-200	0-2 6-8 0.25	1.5 (1.2) 0.4 (0.3) 5 (4)	analogy analogy analogy	0.1 (0.08)	expert	2,740 (2,200) *	1,620 (1,300)
4. Use of paint containing zinc oxide [a)]	spraying full shift short term	100-200 100-200 100-200	2-4 4-6 0.1-0.3	4 (3.2) 2 (1.6) 8 (6.4)	analogy calculated expert	0.5 (0.4)	expert	670 (540) ***	n.e.
5. Zinc die casting [b)]	full shift short term	100-200 100-200	6-8 0.25	1.0 (0.8) 2.0 (1.6)	measured / expert expert	0.1 (0.08)	measured	175 (140) *	85 (70)

Table 4.8 continued overleaf

Table 4.8 continued Conclusions of the occupational exposure assessment

Scenario	Activity	Frequency (days/year)	Duration (hours/day)	Inhalation exposure				Skin exposure	
				Reasonable worst case (mg ZnO/m³) ‡	Method	Typical exposure (mg ZnO/m³) ‡	Method	Reasonable worst case	Typical
6. Brass casting	full shift	100-200	6-8	2.0 (1.6)	measured / expert	0.5 (0.4)		175 (140) *	85 (70)
	full shift, very fine particles (< 0.52 µm)	100-200	6-8	0.2 (0.16)	measured / calculated				
	short term	100-200	0.25	4.0 (3.2)					
	short term, very fine particles (< 0.52 µm)	100-200	0.25	0.4 (0.32)					
7. Welding of zinc coated steel [c)]	full shift	100-200	6-8	0.8 (0.6)	measured	0.1 (0.8)	measured	negl.	n.e.
	short term	100-200	0.25	1.6 (1.3)	expert				

EASE = estimated using EASE
Measured = based upon measured values
Expert = based upon expert judgement
Analogy = based upon measured data for other substances in similar use situations
negl. = negligible
n.e. = not estimated
‡ Data without parenthesis are expressed in mg ZnO/m³, data within parenthesis are expressed in mg Zn/m³
* Based on measured data on zinc compounds
** Based on a combination of information from measured data on zinc compounds, and other substances, including lead and calcium carbonate, partly for the specific scenario and partly for other possibly similar scenarios
*** Based on analogy with other non-volatile substances in paint spraying, assuming a maximum of 12.5% of zinc oxide in paint
a) Inhalation exposure is assumed to be exposure to ZnO resulting from mechanical emission sources, with more than 90% of particles larger than 0.9 µm
b) Inhalation exposure is assumed to be exposure to ZnO resulting from volatilisation of molten zinc metal, with more than 90% of particles larger than 0.9 µm
c) Inhalation exposure is assumed to be exposure to ZnO resulting from volatilisation of molten zinc metal, with a relatively high percentage of small particles (< 1 µm)

4.1.1.3 Consumer exposure

Zinc oxide (micronised or ultra fine) can be used as a totally transparent agent for use in sunscreen preparations. According to Semenzato et al. (1994) the content in most sunscreen emulsions amounted to 5%. Kanda et al. (1989) mentioned a percentage of 20% of ZnO in deodorants. ZnO can be found in paint, inks, lacquers and varnishes, cosmetics, white glue, ointments and as a micronutrient (HSDB, 1998).

Five countries gave some information on consumer products containing zinc oxide, but without quantitative data or more specific uses. Additional to the uses described, the use of zinc oxide in pesticides and as metal surface treatment are mentioned by the Danish Product Register. According to the Finnish Products register the only consumer products seem to be glue for rubber, plastics and wood and sealing paste. Furthermore zinc oxide might be used in dusting powder, as medical astringent, in seed treatment, in white glue and lubricants (according to the US) and in cleaners and car care products (according to Germany).

In Sweden ZnO appears to be a constituent in many types of the consumer products already mentioned in this section. In the majority of these products the content of zinc oxide is reported to be 0-20%.

Apparently zinc oxide 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 fact sheets “verf” (paint) (Bremmer and van Veen, 2000) and “cosmetica” (cosmetics) (Bremmer et al., 2001). These fact sheets 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).

Remark: 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 containing 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 be also 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 indirectly 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 95-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 differ 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 of 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 $\mu g/m^3$ (annual averages). Higher concentrations, up to 14 $\mu g/m^3$, 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) (pers. comm. 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 3.4 µg/l and 443 µg/l (total zinc) have been estimated for the production and processing of zinc oxide, respectively (see Section on local exposure assessment in the environmental part).

Maximum atmospheric zinc concentrations (PEC_{add}s) are 13.1 µg/m^3 and 7.76 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 is 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

Some data were provided on the toxicokinetics of zinc oxide. 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 exposure

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 h post dosing which gradually decreased to about 9% at day 11. The amount of radioactivity retained at 24 h 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 cystein), 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 is 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 h 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 exposure

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 was 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 micronized 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 h. 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 under estimate 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 4.9**. It must be noted that the MPPDep only models deposition, not clearance and retention.

Table 4.9 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 4.9** 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 (halftime 10 min). A small fraction will be subjected 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, tracheobronchial 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 half time 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 half times 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 4.9** is given in **Table 4.10**.

Table 4.10 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 exposure

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 μCi/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 cuticle 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 sub dermal 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 hour 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 theorized 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 4.11**.

Table 4.11 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 exposure

No data available.

Dermal exposure

No data available.

Oral exposure

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 is 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 approx. 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 non-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 non-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 exposure

No data available.

Dermal exposure

No data available.

Oral exposure

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 faecal 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 faeces (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 (approx. 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, mother milk, 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 half time of absorbed radio-labelled zinc has been observed to range from 162 to 500 days. After parenteral administration of $^{65}Zn^{2+}$, half times 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 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 is 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 hypothesized 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 radio-labelled 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

Some data were provided on the toxicokinetics of zinc oxide. 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 faeces, but can also be excreted via urine, saliva, hair loss, sweat and mother milk.

4.1.2.3 Acute toxicity

4.1.2.3.1 Studies in animals

Studies with zinc oxide have been carried out with rats and mice by different routes of exposure. These studies are summarised in **Table 4.12**.

Table 4.12 Acute toxicity

Acute toxicity	Species	Protocol	Results	References
Oral	mouse	unknown	LD_{50} = 7,950 mg ZnO/kg bw	Shumskaya et al. (1986)
	rat	other	LD_{50} > 5,000 mg ZnO/kg bw	Löser (1977)
	rat	other	LD_{50} > 15,000 mg ZnO/kg bw	Löser (1972)
Inhalation	mouse	unknown	LC_{50} = 2.5 g ZnO/m^3 (a)	RTECS (1991)
	rat	other	$LC_{50(4hr)}$ > 5.7 g ZnO/m^3 (b)	Klimisch et al. (1982)
Intraperitoneal	rat	unknown	LD_{50} = 240 mg ZnO/kg bw	Burkhanov (1978)

(a) Exposure time, exposure conditions and particle size unknown
(b) The test compound was Mn^{2+}-containing ZnO (2.8% Mn; 78% Zn; 19.2% O) with a MMAD of 4 µm.

Zinc oxide was administered intragastrically to mice and an LD_{50} of 7,950 mg ZnO/kg bw was determined. The minimal acute toxic dose was 1,000 mg ZnO/kg bw. No more study details were available (Shumskaya et al., 1986).

In an acute toxicity test of Löser (1977) Wistar rats (5/sex) were given a single dose of 5 g ZnO/kg bw (in water) by gavage and observed for 14 days. No mortality and signs of toxicity were observed. The LD_{50} for rats is therefore > 5 g ZnO/kg bw.

In an earlier study of Löser (1972) ten male Wistar rats received a single dose of 15 g ZnO/kg bw by gavage. No mortality occurred. Signs of toxicity were ruffled fur, decreased body weights and diarrhoea. The LD_{50} value for rats was > 15 g ZnO/kg bw.

For the acute inhalation study with zinc oxide in mice (cited in RTECS, 1991) no more details were available. In the study by Klimisch et al. (1982), 10 male and 10 female animals per group were exposed to zinc oxide aerosol (head and nose only) for 4 hours. Aerosol concentration was 5.7 mg/l and the particle size distribution had a mass median aerodynamic diameter of 4 µm ± 2.9 (GSD). Only one concentration and a control group were tested. All animals survived up to day 14 post exposure. Apart from a dusty fur on the head the day after the exposure, no effects were seen. Body weights developed normally. At pathological examination all organs were normal. The LC_{50} was > 5.7 mg/l.

In a study by Burkanov (1978) rats were exposed intraperitoneally to zinc oxide and the LD_{50} value was determined to be 240 mg ZnO/kg bw. No more study details were available.

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

Additional single dose studies

In a lung function test using 23 guinea pigs that were exposed by inhalation to 0.9 mg ZnO/m^3 (furnace-generated aerosol; 0.05 microns) for 1 hour a progressive decrease in lung compliance was observed (from 9% below control value at the end of exposure to 16% after one hour post-exposure), but no change in air flow resistance (Amdur et al., 1982). In contrast to these results, no effects on ventilation, lung mechanics, diffusing capacity of carbon monoxide, or most lung volume parameters were observed in another lung function test with 10 guinea pigs exposed for 3 hours to 7.8 mg ZnO/m^3 (furnace-generated aerosol; 0.05 microns). However functional residual capacity was significantly decreased (10% below control value) with only minimal changes in other lung volume subdivisions (Lam et al., 1982).

Gordon et al. (1992) studied the effects of inhaled zinc oxide in guinea pigs, rats, and rabbits. Animals were exposed to 0, 2.5 or 5 mg ZnO/m^3 (furnace-generated aerosol; 0.06 microns) for up to 3 hours and their lungs lavaged at 24 hours thereafter. The lavage lung fluid of both guinea pigs and rats exposed to the highest dose showed significant increases in total cells (guinea pigs 2.5-fold; rats 2-fold), lactate dehydrogenase (guinea pigs 24-fold, rats 9-fold), β-glucuronidase (guinea pigs 13-fold; rats 27-fold), and protein content (guinea pigs 3.5-fold and rats 5.6-fold). Exposure of guinea pigs to 2.5 mg ZnO/m^3 for 3 hours resulted in significant increases in LDH (16-fold), β-glucuronidase (5-fold), and protein (1.4-fold). Exposure of rats to 2.5 mg ZnO/m^3 resulted in significant increases in lactate dehydrogenase (4.5-fold), β-glucuronidase (11-fold), and protein (5-fold). Rabbits, exposed to 2.5 or 5 mg ZnO/m^3 (furnace-generated aerosol; 0.06 microns) for 2 hours, showed no changes in the biochemical or cellular parameters.

4.1.2.3.2 Studies in humans

No data are available on commercially grade zinc oxide.

Very specific operations using very high temperatures such as cutting or welding of galvanised steel (see the risk assessment report on zinc metal) can give rise to the formation of fumes containing ultra fine particulate zinc oxide (< 0.1 micron in diameter). Exposure to these fumes can cause metal fume fever, expressing itself in certain typical symptoms including a dry and sore throat, fever, coughing, dyspnoea, pyrexia, muscular pains, headache and metallic taste

(Heydon and Kagan, 1990; Gordon et al., 1992; Mueller and Seger, 1985). In addition to these symptoms, gastrointestinal disturbance may be associated with exposure to ultra fine particulate fumes (NIOSH, 1975).

A number of studies have measured exposure levels associated with metal fume fever. In a study by Gordon et al. (1992) humans (n = 4) were exposed in a single-blind fashion to control furnace gases or ultra fine ZnO particles (5 mg/m^3) for 2 hours. All 4 persons exposed to ZnO showed the typical metal fume fever symptoms beginning 4 to 8 hours after exposure and disappearing within 24 hours. The reported symptoms included fever, chills, dry or sore throat, chest tightness, and headache. No changes were observed in pulmonary function immediately after exposure. The specific airway resistance increased with 16% in all subjects exposed to ZnO.

Marquart et al. (1989) investigated the effects of occupational exposure for 6-8 hours to zinc oxide fume generated during welding operations. Spirometric lung-function measurements were conducted 5 days before and after the work shift of 11 welders of zinc-coated steel, ten non-welders who were indirectly exposed to welding fumes, and 17 controls. The personal exposure to zinc was monitored using PAS-6 samplers. The geometric mean concentration for welders was 0.034 mg Zn (as ZnO)/m^3, for exposed non-welders 0.019 mg ZnO/m^3, and for controls 0.004 mg ZnO/m^3. No changes in lung function parameters were observed at a 5% significance level. No symptoms of metal fume fever were reported.

Blanc et al. (1991) studied also the response in humans after exposure to zinc welding fume. Fourteen welders were acutely exposed to zinc oxide welding fume over a 15- to 30-minute period. The personal exposure to zinc oxide was monitored and the mean cumulative exposure was 2.3 ± 1.7 g.min/m^3 resulting in an exposure of 77-153 mg ZnO/m^3. Pulmonary function, airway reactivity, serum zinc levels and blood cell counts were measured. A bronchoalveolar lavage (BAL) was carried out to assess the cellular inflammatory response in the lung. Changes in pulmonary function and measured airway resistance were minimal. Cumulative zinc exposure and polymorphonuclear leukocyte count were positively correlated. A significant dose-dependent increase of immunological activity (i.e. increased polymorphonuclear leukocytes) was found in the BAL fluid 22 hours after exposure.

In another study by Blanc et al. (1993), 26 experimental welding fume exposures in 23 volunteers, with a representative range of welding experience, were carried out. Subjects performed electric arc welding on galvanized mild steel over a 15- to 30-minute period. Post exposure BAL was performed at 3, 8, or 22 hours after exposure in 6, 11, and 9 subjects, respectively, and compared with BAL obtained from 17 control subjects. The mean zinc exposures were 1.8, 2.0, and 2.6 g.min/m^3 for the groups lavaged after 3, 8, and 22 hours, respectively, resulting in an exposure of 20-170 mg zinc/m^3 (equal to 25-212 mg ZnO/m^3; calculation based on a 30-minute exposure to the reported exposure range of 0.6-5.1 g.min/m^3). Besides inflammatory cells, BAL fluid supernatant concentrations of several cytokines, i.e. tumour necrosis factor (TNF), interleukin-6 (IL-6), and interleukin-8 (IL-8) increased in time and exposure-dependent fashion after zinc oxide welding fume exposure.

In a study by Kuschner et al. (1995), 14 volunteers were studied after inhalation exposure to purified zinc oxide fume and after sham exposure to air. The exposure concentrations ranged from 2.76-37 mg zinc/m^3 (3.4-46 mg ZnO/m^3) for a period of 15 to 120 minutes (cumulative zinc exposure 165-1,110 mg.min/m^3). Twenty hours after exposure BAL was performed and analysed for cell contents and cytokines including TNF, IL-8, and interleukin-1 (IL-1). Polymorphonuclear leukocytes were significantly increased in the BAL fluid obtained post-exposure compared to sham. Cumulative zinc exposure correlated positively with changes in

BAL supernatant concentrations of both TNF ($r^2 = 0.58$) and IL-8 ($r^2 = 0.44$). Cigarette smoking was not associated with differences in BAL TNF or IL-8. The authors concluded that the data suggest a threshold for zinc exposure-related increased TNF and IL-8 at approximately 500 mg.min/m^3 expressed as zinc (625 mg.min/m^3 as ZnO). However, the correlation coefficients between cumulative exposure levels and rise in TNF or IL-8 were low. The rapporteur has analysed the data also for the presence of a concentration-effect relationship, but these correlation coefficients appeared to be even lower. A definite conclusion whether the onset of metal fume fever is governed by the cumulative exposure rather than the exposure concentration can therefore not be drawn due to the limited amount of data points and the rather large variability of the data. Hence it is impossible to derive a NOAEL for metal fume fever from this study with reasonable certainty. Therefore, the data are not considered superior to those of Gordon et al. (1992), from which a 5 mg ZnO/m^3 effect level for metal fume fever was derived.

Other reports have addressed the etiology of metal fume fever as well, e.g. Barceloux (1999), and Kelleher et al. (2000). However, these studies, as well as several case reports (e.g. Vogelmeier et al., 1987; Langham Brown, 1988; Malo et al., 1990; Ameille et al., 1992) do not allow the establishment of a clear NOAEL for metal fume fever either.

As stated above, metal fume fever is restricted to very specific operations using very high temperatures such as cutting or welding of galvanised steel. It is not related to the production and use of commercial grade zinc oxide. Metal fume fever is exclusively associated with freshly formed ultra fine particulate zinc oxide (< 0.1 μm). As these ultra fine particles rapidly agglomerate to bigger particles, which are normally encountered at production and processing sites, at these sites there is no indication for metal fume fever.

By means of a questionnaire all zinc companies were asked for the incidence of metal fume fever at their site over the past decades of operation. The occupational hygienist was asked to check on this matter in routinely carried out medical surveillance programs. Eleven companies (mainly zinc oxide producers) reported back. According to this survey it appears that there have been no observations of zinc metal fume fever over the last decade nor in recent occupational practice, i.e. at the exposure levels of the zinc producing and using industry of today.

4.1.2.3.3 Conclusion on acute toxicity

Based on the available data it can be concluded that zinc oxide has low acute toxicity after oral and inhalation exposure. According to EC criteria zinc oxide needs not to be classified on the basis of its acute toxicity after oral and inhalation exposure.

Symptoms of metal fume fever (headache, fever, leukocytosis) have been observed in humans acutely exposed to ultra fine particulate zinc oxide in welding fumes; at 0.034 mg Zn/m^3 (as ZnO) no effects were reported. In another study, all 4 persons exposed to control furnace gases or ultra fine ZnO particles (5 mg ZnO/m^3) for 2 hours showed the typical metal fume fever symptoms beginning 4 to 8 hours after exposure and disappearing within 24 hours. Since no studies are available that allow the establishment of a NOAEL for metal fume fever with a reasonable degree of certainty, this LOAEL (5 mg ZnO/m^3) is taken forward to the risk characterisation. It is noted that exposure to ultra fine particulate zinc oxide is not related to commercial grade zinc oxide but almost exclusively relates to very specific operations such as cutting or welding of galvanised steel. According to the response from 11 zinc companies to a questionnaire, there have been no observations of zinc metal fume fever over the last decade and in recent occupational practice.

4.1.2.4 Irritation

4.1.2.4.1 Skin irritation

Studies in animals

In a study using 2 NZW rabbits (Löser, 1977), no dermal reactions were noted after the application (ear) of 500 mg ZnO/animal during 24 hours under occlusion. The observation period was 7 days.

No signs of skin irritation were noted in open patch tests on the dorsal skin (5 cm^2) of mice (n = 6), guinea pigs (n = 8) and rabbits (n = 4) when they were exposed daily to 0.5 ml ZnO (as 20% suspension in 0.1% Tweet 80, pH = 7.4) for 5 consecutive days (Lansdown, 1991). In rabbits (n = 4) also an occlusive patch test with 0.5 ml of the same test substance was performed, showing negative results for skin irritation (Lansdown, 1991).

Studies in humans

No signs of skin irritation were noted when an occlusive 25% zinc oxide patch (2.9 mg Zn/cm^2) was placed on the human skin for 48 hours (Agren, 1990). The zinc oxide was incorporated in the adhesive (natural rubber, gum rosin and white mineral oil; all pharmaceutical quality) of the patch.

Derry et al. (1983) observed a rash and follicular pustules developing in a patient who received a treatment with a 40% zinc oxide ointment treatment (15 g on 150 cm^2) under occlusive dressing at 24 h post treatment. The dermal reaction disappeared 2 days after removal of the ointment and treatment with cool saline compresses, but reappeared after application of 5% zinc oxide. From the study it could not be derived whether the dermal effects were a result of zinc oxide or from other treatment-related stimuli. In 5 other patients who were treated with 40% zinc oxide ointment in a similar way and in 6 volunteers who received 100 g of 40% zinc oxide ointment on chest and legs, no signs of dermal reactions were reported.

4.1.2.4.2 Inhalation exposure

No data are available for irritation after inhalation exposure. Whereas data based on single (Section 4.1.2.3) and repeated (Section 4.1.2.7.1) inhalation exposure to ultra-fine zinc oxide fumes show changes in pulmonary function and induction of airway inflammatory responses, a well-performed acute inhalation toxicity study in rats (Klimisch et al. (1982), see Section 4.1.2.3.1) did not yield any indication for signs of upper airway irritation from commercial zinc oxide aerosol (particle size: MMAD 4 μm ± 2.9 (GSD)).

4.1.2.4.3 Eye irritation

In an eye irritation study in 2 NZW rabbits (Löser, 1977) 50 mg ZnO/animal caused erythema (mean scores over 24-72 hours: 3 and 2) and edema (mean scores over 24-72 hours: 1.3 and 0.3) up to 48 hours after treatment. In the first rabbit erythema persisted for 7 days. No effects were seen on the iris and cornea. Zinc oxide is borderline positive for irritation to the rabbit eye in this study.

In another eye irritation study using 2 NZW rabbits 50 mg ZnO/animal (Thijssen, 1978) caused slight erythema (mean scores over 24-72 hours: 0.7 and 0.7) of the conjunctiva that lasted for 2 days. No effect on the iris or cornea was seen in the 7-day observation period. Zinc oxide is not irritating to the rabbit eye in this study.

In a well-performed eye irritation/corrosion study, performed according to Directive 92/69/EEC B.5 and OECD guideline 405, three male New Zealand White rabbits were treated by instillation of approximately 64 mg of zinc oxide (a volume of about 0.1 ml) into the Conjunctival sac of one eye. The other eye remained untreated and served as control. After 24 hours, both eyes of two animals were rinsed with water. The eyes were examined at 1, 24, 48 and 72 hours after instillation.

No symptoms of systemic toxicity were observed and no mortality occurred. Slight iridial irritation (grade 1) was observed in one animal, at 1 hour only. Slight irritation of the conjunctivae (grade 1-2) was seen as redness (mean scores over 24-72 hours 0.7, 1 and 1), which had completely resolved at 72 hours in all animals. Chemosis (grade 2) and discharge (grade 1) were also observed in all animals, but at 1 hour only. No corneal opacity or epithelial damage was observed in any of the animals (Van Huygevoort, 1999a).

4.1.2.4.4 Conclusion on irritation

Although the skin irritation studies do not comply with current guidelines it is considered that the data are acceptable. According to EC criteria the substance needs not to be classified as irritant to the skin.

Although single and repeated inhalation exposures to ultra fine zinc oxide fumes showed changes in pulmonary function and induced airway inflammation, a well-performed acute inhalation study in rats with commercial grade ZnO did not show any signs of upper airway irritation and therefore the substance does not require classification as irritant to the respiratory system.

Based on the findings in eye irritation studies (of which one a well-performed study according to EU and OECD guidelines), zinc oxide is considered not irritating or corrosive to the eyes and, therefore, does not have to be classified/labelled.

4.1.2.5 Corrosivity

The substance is not corrosive to the skin, eyes and respiratory tract (see Section 4.1.2.4).

4.1.2.6 Sensitisation

4.1.2.6.1 Studies in animals

The skin sensitising potential of zinc oxide (purity 99.69%) was investigated in female Dunkin Hartley guinea pigs in two well-performed maximisation tests, conducted according to Directive 96/54/EC B.6 and OECD guideline 406. Based on the results of a preliminary study, in the main studies experimental animals (10 in each test) were intradermally injected with a 20% concentration and epidermally exposed to a 50% concentration (i.e. the highest practically

feasible concentration). Control animals (5 in each test) were similarly treated, but with vehicle (water) alone. Approximately 24 hours before the epidermal induction exposure all animals were treated with 10% SDS. Two weeks after the epidermal application all animals were challenged with a 50% test substance concentration and the vehicle.

In the first study, in response to the 50% test substance concentration skin reactions of grade 1 were observed in 4/10 experimental animals 24 hours after the challenge (40% sensitisation rate), while no skin reactions were evident in the controls. In contrast, in the second study no skin reactions were evident in the experimental animals (0% sensitisation rate), while a skin reaction grade 1 was seen in one control animal. The skin reaction observed in one control animal is probably a sign of non-specific irritation (Van Huygevoort, 1999b1; 1999b2).

In a third well-performed maximisation test, conducted according to the same guidelines and with the same experimental design, another analytical grade zinc oxide was tested (Zincweiß Pharma A; purity 99.9%). The only difference with the studies described above was the intradermal induction concentration, which was 2% as for Zincweiß Pharma A this was considered the highest concentration that could reproducibly be injected. In this test no skin reactions were evident in both experimental and control animals, hence a 0% sensitisation rate for Zincweiß Pharma A. White staining of the treated skin by the test substance was observed in some animals 24 and 48 hours after challenge (Van Huygevoort, 1999i).

4.1.2.6.2 Studies in humans

In a human patch test performed with 100 selected leg-ulcer patients, 11/100 patients gave an allergic reaction with zinc ointment (60% ZnO and 40% sesame oil). However, 14/81 patients gave a positive response when treated with sesame oil alone (Malten and Kuiper, 1974). This study does not give any indication for a skin sensitising potential of zinc oxide in humans.

Söderberg et al. (1990) studied the effect of zinc oxide on contact allergy to colophony. With 14 patients with earlier history of moderate patch test reactions to colophony a patch test with 10% ZnO (2.3 mg Zinc/cm²) with and without colophony was performed. No positive response was observed in the 14 patients when only a 10% solution of zinc oxide was used. The addition of zinc oxide to colophony decreased the allergic reaction induced by colophony.

4.1.2.6.3 Conclusion on sensitisation

The data submitted fulfil the base-set requirements for skin sensitisation testing. While some studies with guinea pigs produced conflicting results, the weight of evidence does not indicate that zinc oxide is a very potent sensitising agent in animals, if any. In addition, the results of human patch tests do not indicate that zinc oxide acts as a sensitising agent in humans, either. Zinc oxide does not have to be classified/labelled for skin sensitisation. This is supported by the fact that zinc compounds, especially zinc oxide and zinc distearate, have been used for over decades in a variety of pharmaceutical and cosmetic products (some of them even dermatological preparations against skin irritation) without any such reported effects.

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

Some data were provided on the repeated dose toxicity of zinc oxide. 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 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 are summarised in **Table 4.13**.

Table 4.13 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 $ZnSO_4 \cdot 7\ H_2O$ /kg feed daily via diet for 13 weeks	NOAEL 3,000 mg/kg feed At 30,000 mg/kg feed: haematological 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 $ZnSO_4 \cdot 7\ H_2O$/kg feed daily via diet for 13 weeks	NOAEL 3,000 mg/kg feed At 30,000 mg/kg feed: haematological 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-week 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.

4.1.2.7.2 Additional studies in animals

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 $\approx$ 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 BChE (Butyrylthiocholine-esterase). The activities of TTPase (thiamine pyrophophatase) 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 heamogram 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 ultra fine 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; they 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 characterized 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 ultra fine 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 ultra fine (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 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).

4.1.2.7.3 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 7th 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 heamatotoxicity, 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 US 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 proceeded 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 pertubations 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.

4.1.2.7.4 Conclusion on repeated dose toxicity

Some data were provided on the repeated dose toxicity of zinc oxide. 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.

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 ultra fine 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 ultra fine ZnO/m^3 (3 hours/day for 5 days) did not alter the lung function parameters in guinea pigs but at 7 mg ultra fine ZnO/m^3 (3 hours/day for 5 days) or at 5 mg ultra fine 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 6794 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* studies and one *in vivo* study were provided on the genotoxicity of zinc oxide. 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 4.14**.

Table 4.14 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)*
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)*

Table 4.14 continued overleaf

Table 4.14 continued Mutagenicity data

Genetic toxicity	Species	Protocol	Results	Form	Reference
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. 5–20 µg/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)
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)*

Table 4.14 continued overleaf

Table 4.14 continued Mutagenicity data

Genetic toxicity	Species	Protocol	Results	Form	Reference
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 h 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 were 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 oxide. 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 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. 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) 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 are 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 Standardized 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 an 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's 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

Some data were provided on the reproductive toxicity of zinc oxide. 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).

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 4.15** 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 4.15 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; out bred 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.

Twelve 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 where 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

Some data were provided on the reproductive toxicity of zinc oxide. 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.

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 manifested 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 is considered end-points 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 oxide at the workplace, from uses of consumer products and indirectly via the environment (see Section 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 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.

Some data were provided on the toxicokinetics of zinc oxide. 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 mother milk.

Zinc oxide has low acute toxicity after oral and inhalatory exposure. Zinc oxide is not a skin irritant, and based on the findings in eye irritation studies (of which one a well-performed study according to EU and OECD guidelines) zinc oxide is considered not irritating/corrosive to the eyes. Although single and repeated inhalation exposures to ultra fine zinc oxide fumes showed changes in pulmonary function and induced airway inflammation (metal fume fever), no studies are available that allow the establishment of a NOAEL for metal fume fever with a reasonable degree of certainty. Therefore, the LOAEL of 5 mg ZnO/m^3 obtained from a human volunteer study is used in the risk characterisation. It is noted that exposure to ultra fine particulate zinc oxide is not related to commercial grade zinc oxide but almost exclusively relates to very specific operations such as cutting or welding of galvanised steel.

Data in guinea pigs and humans indicate that zinc oxide is not a very potent sensitising agent in animals, if any, and is not a sensitising agent in humans. This is supported by the fact that zinc compounds, especially zinc oxide and zinc distearate, have been used for over decades in a variety of pharmaceutical and cosmetic products (some of them even dermatological preparations against skin irritation) without any such reported effects.

Some data were provided on the repeated dose toxicity of zinc oxide. 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.

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 ultra fine 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 ultra fine ZnO/m^3 (3 hours/day for 5 days) did not alter the lung function parameters in guinea pigs but at 7 mg ultra fine ZnO/m^3 (3 hours/day for 5 days) or at 5 mg ultra fine 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.

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 oxide. 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.

Some data were provided on the reproductive toxicity of zinc oxide. 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.

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 end-points 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 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 “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 characterization for workers is limited to the dermal and inhalation routes of exposure. Workers are exposed by inhalation to zinc oxide dust during the production of zinc oxide (Scenario 1), the production of paints and rubber products containing zinc oxide (Scenarios 2 and 3, respectively), and zinc die casting (Scenario 5). During the use of paints containing zinc oxide (Scenario 4) respiratory exposure to dust in a matrix (suspension / solution) is possible. In the other two scenarios (Scenario 6, brass casting; Scenario 7, welding of zinc coated steel) respiratory exposure partly concerns aerosols possibly containing a relatively large amount of very fine particles, with a much smaller particle size than dusts. Actual exposure is in most situations exposure to coagulated aerosols and not to very fine dusts. Welding fumes, however, are known to consist of a large percentage of very small particles.

With regard to exposure via the skin in Scenario 1-3 and 5-7 it concerns dermal contact with dusts, but in Scenario 4 exposure to zinc oxide in solutions or suspensions is possible. For risk

assessment the reasonable worst-case exposure levels as well as the physical form will be taken into account (dust, fumes, solutions/suspensions).

4.1.3.2.1 Acute toxicity

For occupational risk assessment the short-term inhalation exposure levels to zinc oxide dust of 1.6-10 mg/m^3, (see Table 4.8) are compared with the LC_{50} values in mice (2,500 mg/m^3) and rats (> 5,700 mg/m^3). 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 values are calculated for a severe effect (lethality). Given the calculated MOS values (250-1,562 for the mice data, > 570 - > 3,562 for the rat data) it is expected that there is no risk for lethality after inhalation exposure: **conclusion (ii)**.

However, for Scenario 6 and 7 a risk assessment for metal fume fever might be relevant for short-term inhalation exposure, because these scenarios possibly concern exposure to very fine particles. Metal fume fever is related to the ultra fine particle fraction of the fume. Metal fume fever symptoms were observed in humans exposed for 2 hours to 5 mg/m^3. In Scenario 6 a short-term exposure to such particles (< 0.52 μm) of 0.4 mg ZnO/m^3 is calculated from measured exposure levels. Welding fumes are known to consist of a large percentage of very small particles. Since specific data on particle size distribution is missing, it is assumed that the exposure in Scenario 7 is relevant for the occurrence of metal fume fever. The short-term inhalation exposure level in Scenario 7 is 1.6 mg/m^3. The resulting MOS values for metal fume fever for Scenario 6 and Scenario 7 are 12.5 and 3, respectively, based on an effect level. Therefore it is concluded that zinc oxide is only of concern after inhalation exposure in Scenario 7: **conclusion (iii)**.

Acute toxicity studies performed by dermal administration are not available. As the oral toxicity study with zinc oxide has an LD_{50} > 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

Acute dermal irritation

Because no signs of irritation were observed in the skin irritation studies with rabbits, mice, guinea pigs, and humans it is concluded that zinc oxide is of no concern for workers with regard to acute skin irritation: **conclusion (ii)**.

Eye irritation

Exposure to the eyes is possible via fumes or dust. Based on a well-performed eye irritation study carried out with zinc oxide it can be concluded that zinc oxide is not irritating or corrosive to the eyes. Therefore, it is concluded that exposure to zinc oxide of no concern for workers with regard to acute eye irritation (see Section 4.1.2.4) and that **conclusion (ii)** is applicable.

Acute respiratory irritation

Based on a well-performed acute inhalation study with commercial grade 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 Corrosivity

Given the results from the skin and eye irritation studies, it is concluded that zinc oxide is of no concern for workers with regard to corrosivity: **conclusion (ii)**.

4.1.3.2.4 Sensitisation

From animal data and human experience it can be concluded that zinc oxide is of no concern for workers with respect to sensitisation: **conclusion (ii)**.

There are neither data from human experience nor other data with respect to possible respiratory sensitisation.

4.1.3.2.5 Repeated dose toxicity

Because there are no relevant dermal and respiratory repeated dose toxicity studies available, risk characterisation for local skin and respiratory effects after repeated exposure to zinc oxide cannot be described and it is unknown whether local or systemic effects of ZnO are critical. Risk characterisation is limited to the systemic effects of the Zn^{2+}-ion.

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 4.1.2.2.1)). The occupational health risk due to the ZnO exposure is determined by comparing the internal NOAEL of 10 mg Zn^{2+}/day with the internal occupational exposure.

The dermal and respiratory exposure levels of ZnO for the occupational scenarios (see Section 4.1.1.2 and **Table 4.8**) are estimated. The reasonable worst-case exposure 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. For zinc oxide, a 20% respiratory absorption is chosen (see Section 4.1.2.2). For dermal absorption to zinc oxide in solutions / suspensions in Scenario 4 2% is taken into account, whereas 0.2% is applied for exposure to zinc oxide via dusts in the other scenarios.

The MOSs between the internal NOAEL and the internal occupational exposure estimates are mentioned in **Table 4.16**. 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 4.16 Occupational risk assessment of zinc oxide for repeated dose toxicity after dermal and inhalation exposure (systemic effects)

	Risk characterisation for dermal and inhalation exposure			
Scenario / subscenario #	**Estimated external dermal exposure in mg Zn^{2+}/day (between brackets internal exposure in mg Zn^{2+}/day) a)**	**MOS b)**	**Estimated external inhalation exposure in mg Zn^{2+}/m^3 (between brackets internal exposure in mg Zn^{2+}/day) c)**	**MOS b)**
1: Production	2,200 (4.4)	2.3	-	-
- Production d)			3.9 (7.8)	1.3
- Recycling			3.9 (7.8)	1.3
- Workplace 1			1.7 (3.4)	2.9
- Workplace 2			1.6 (3.2)	3.1
- Work place 3			1.6 (3.2)	3.1
- Work place 4			4.3 (8.6)	1.2
2: Production of paints containing zinc oxide	2,400 (4.8)	2.1	2 (4)	2.5
3: Production of rubber products containing zinc oxide	2,200 (4.4)	2.3	0.3 (0.6)	17
4: Use of paint containing zinc oxide	540 (10.8)	0.9	1.6 (3.2)	3.1
5: Zinc die casting	140 (0.3)	33	0.8 (1.6)	6.3
6: Brass casting				
- Full shift	140 (0.3)	33	1.6 (3.2)	3.1
- Full shift; very fine particles	-	-	0.16 (0.32)	31
7: Welding of zinc coated steel	Negl. (negl.)	high	0.6 (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 dumping and spraying. It is noted that possible higher risks resulting from daily performance of these activities associated with higher short-term exposures, are not accounted for.

a) Estimated internal dermal exposure to Zn^{2+} used for calculating the risk, assuming a dermal absorption of 2% for solutions/suspensions in Scenario 4 and 0.2% for dust in the other scenarios).

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 20%, a respiratory volume of 10 m^3 for a worker/day.

d) All data, except recycling, combined.

Given the calculated MOS values for dermal and inhalation exposure as mentioned in **Table 4.16**, it is concluded that, based upon the present information, health risks due to occupational dermal exposure cannot be excluded in Scenario 4 (use of paints) **conclusion (iii)**.

There is no concern in the other exposure situations: **conclusion (ii)**.

Based on the typical exposure estimates for inhalation exposure in the different scenarios, no adverse health effects are expected to occur.

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 favors this assumption,
- the human study was not performed with ZnO, 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 16.6 mg ZnO/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 B). The calculated MOSs range from 34-high and 43-1,163 for dermal and inhalation exposure, respectively. Comparing these values with the minimal MOS of 360, 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 1.2-14 mg Zn^{2+}/day (see **Table 4.17**) compared to the internal NOAEL of 10 mg Zn^{2+}/day results in **conclusion (iii)** for Scenario 1 (production; recycling; workplace 4) and Scenario 4 (use of paint containing zinc oxide) (calculated MOS values 0.8 and 0.7, respectively). Based on the typical exposure estimates for inhalatory exposure, adverse health effects are not expected to occur due to combined exposure in Scenario 1, but cannot be excluded in Scenario 4.

Table 4.17 Occupational risk assessment of zinc oxide for repeated dose toxicity after combined dermal and inhalation exposure

	Risk characterisation for dermal and inhalation exposure			
Scenario / subscenario#	**Estimated internal dermal exposure in mg Zn^{2+}/day a)**	**Estimated internal inhalation exposure in mg Zn^{2+}/day a)**	**Combined internal exposure in mg Zn^{2+}/day**	**MOS b)**
1: Production	4.4	-	-	-
- Production c)		7.8	12.2	0.8
- Recycling		7.8	12.2	0.8
- Workplace 1		3.4	7.8	1.3
- Workplace 2		3.2	7.6	1.3
- Work place 3		3.2	7.6	1.3
- Work place 4		8.6	13.0	0.8
2: Production of paints containing zinc oxide	4.8	4	8.8	1.1
3: Production of rubber products containing zinc oxide	4.4	0.6	5.0	2
4: Use of paint containing zinc oxide	10.8	3.2	14.0	0.7
5: Zinc die casting	0.3	1.6	1.9	5.3
6: Brass casting - Full shift	0.3	3.2	3.5	2.9
7: Welding of zinc coated steel	Negl.	1.2	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 dumping and spraying. It is noted that possible higher risks resulting from daily performance of these activities associated with higher short-term exposures, are not accounted for.

a) See Table 4.15 for derivation of internal exposure values.

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

c) All data, except recycling, combined.

4.1.3.2.6 Mutagenicity

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

4.1.3.2.7 Carcinogenicity

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

4.1.3.2.8 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)**.

4.1.3.2.9 Occupational Exposure Limits

The ACGIH established a TWA for fumes in 1962 (5 mg/m^3), a TWA for dust in 1988 (10 mg/m^3), and a STEL for fumes in 1976 (10 mg/m^3), which were revised in 1992 (see **Table 4.1**). The TWA for fumes was based on that the incidence of metal fume fever will be low at this concentration and that the cases that may occur will be mild. Based on animal data, the NOAEL for pulmonary and small airway inflammation in guinea pigs was 2.7 mg/m^3, zinc oxide fumes is currently under review again. The TWA for dust was based on the minor adverse effects on the lung and no significant occurrence of metal fume fever when exposures are kept under reasonable control. No data are available to quantify the STEL.

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

The occupational limit values as described above are predominantly based on the occurrence of metal fume fever and irritation. However, in the present report reference is made to more recent studies on metal fume fever, indicating effects at concentrations at the level of the current OELs, which should be taken into account for the establishment of OELs. Therefore, it is recommended to reconsider the current OELs. Furthermore, a European OEL is lacking while exposure is possible and in some cases leading to a conclusion (iii); therefore, the establishment of a European OEL should be considered.

4.1.3.3 Consumers

Table 4.18 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

Zinc oxide can be used in baby care ointments leading to a zinc exposure of 0.33 mg/day. It is also used in sunscreens for which a consumer exposure of 2.14 mg zinc/day was calculated based on a high ZnO percentage of 10%, referring to a very high protection factor. A zinc oil containing 60% ZnO, with an estimated exposure of 2.62 mg zinc/day, will only be medically used to treat skin disorders.

4.1.3.3.1 Acute toxicity/Irritation/Corrosivity/Sensitisation

Given the data available, it is concluded that zinc oxide 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.

When all consumer products containing zinc oxide (except the medically used zinc oil containing 60% zinc oxide) are taken into account, the internal exposure by the use of these products will be approximately 2.5 mg zinc/day. The MOS between this internal exposure and the (internal) NOAEL is 4.

However, not all consumer products containing zinc oxide are 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 4.18**). 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 oxide 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 oxide 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 oxide 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

<u>General exposure</u>

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 inhalation and oral absorption (20% and 12%, respectively), and by assuming a breathing volume of 20 m^3/day and a drinking water consumption of 2 l/day (see **Table 4.19**).

Table 4.19 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	3.4	0.00082	13.1	0.052
Processing	443	0.11	7.76	0.031

Comparing the (internal) NOAEL with the internal exposures, MOSs are in the range 91-12,195. 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 water.

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 oxide 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 concer for carcinogenicity: **conclusion (ii)**.

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

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

Effects assessment: Hazard identification

Explosivity

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

Flammability

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

Oxidising potential

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

Risk characterisation

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

5 RESULTS

5.1 ENVIRONMENT

(To be added later)

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.

This conclusion is reached, because:

- metal fume fever due to acute inhalation exposure cannot be excluded in occupational exposure Scenario 7 (welding of zinc coated steel),
- systemic effects after repeated dermal exposure at the workplace cannot be excluded in Scenario 4 (use of paint containing zinc oxide). Besides, health risks due to combined exposure in Scenario 1 (production of zinc oxide; recycling; work place 4) and Scenario 4 cannot be excluded too.

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		Scenario 3		Scenario 4		Scenario 5		Scenario 6		Scenario 7	
	MOS	Conclusion	MOS	Conclusion	MOS	Conclusion	MOS	Conclusion	MOS	Conclusion	MOS	Conclusion	MOS	Conclusion
Acute toxicity														
- Dermal	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii
- Inhalation	> 250	ii	> 250	ii	> 500	ii	> 313	ii	> 1,250	ii	> 625 12.5	Ii ii [a]	> 1,562 3	Ii **iii** [a]
Irritation, single exposure														
- Dermal	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii
- Inhalation	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii
- Eyes	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii
Sensitisation														
- Dermal	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii
- Inhalation	n.a.	ii	n.a.	Ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii
Repeated dose toxicity, systemic effects														
- Dermal	2.3	ii	2.1	ii	2.3	ii	0.9	**iii**	33	ii	33	ii	high	ii
- Inhalation	1.2-3.1	ii	2.5	ii	17	ii	3.1	ii	6.3	ii	3.1/31	ii	8.3	ii
- Combined	0.8-1.3	**iii** [b]/ ii	1.1	ii	2	ii	0.7	**iii**	5.3	ii	2.9/16	ii	8.3	ii
Mutagenicity	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii
Carcinogenicity	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii
Reproductive toxicity, fertility	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii
Developmental effects														
- Dermal	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii
- Inhalation	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii
- Combined	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii

a) Metal fume fever
b) Conclusion (iii) applicable for “production” (i.e. all data, except recycling, combined), “recycling”, and “workplace 4”

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 oxide is considered not to form a risk with respect to explosive, flammable and oxidising properties.

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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 Measured data of zinc oxide in zinc alloy die casting

Table A1 Exposure to zinc oxide in zinc die casting

Substance	Industries and tasks	Number of samples / persons	Exposure levels (mg Zinc / m³) full shift	Reference / remarks
ZnO fumes	melting and casting	61	0.73-0.87	Company G (1996)
Zn	melting and casting	76	AM (Range) 1993: 0.0245 (0.001-0.163) 1994: 0.0904 (0.016-0.158) 1995: 0.0629 (0.016-0.163)	Company R (1996)
Zn	casting	1	AM (Range) 1994: 0.247 (0.02-1.0) 1995: 0.06 ()	Company U (1996)
ZnO	casting	19	0.02-17	HSE (2000)
Zink and zinc compounds	Drehrorofen Schmelzofen	1 1 1 1	0.077 0.054 0.13 0.015	EBCR (2000)

n.a. = Not available. In column three one sample per person is generally assumed

Table A2 Exposure to zinc oxide in brass casting

Substance	Industries and tasks	Number of samples / persons	Exposure levels (mg Zinc/m³) full shift	Reference / remarks
In dust	zinc alloy die casting		(All values AM)	Industry E (1996)
	above machine pot	n.a.	0.4	Foundry A
		n.a.	0.1	duration not given
		n.a.	0.83	
	above remelt pot	n.a.	0.44	
	personal	n.a.	0.36	
	above machine pot	n.a.	0.78	Foundry B
		n.a.	0.26	duration 480-540 min
		n.a.	2.08	
	above remelt pot	n.a.	2.16	
		n.a.	0.2	Foundry C
	above machine pot	n.a.	2.35	duration 300-570 min.
		n.a.	2.8	
		n.a.	3.02	
		n.a.	3.3	
	above bulk melter	n.a.	1.26	
		n.a.	0.91	personal
		n.a.	1.38	
		n.a.	0.31	

Table A.2 continued overleaf

Table A2 continued Exposure to zinc oxide in brass casting

Substance	Industries and tasks	Number of samples / persons	Exposure levels (mg Zinc/m^3) full shift	Reference / remarks
Zn	brass casting	70 workers		Company AD (1999) batchwise process
	< 1998		3-5	continuous process
	1998 and later		< 0.1	
Total inhalable mg Zinc/m^3	brass casting		AM (range)	Groat et al (1999)
		4	0.7 (0.1-0.4)	Site 1
		4	7.7 (2.5-16.8)	Site 2

Appendix B 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 ZnO exposure is the NOAEL of 31.52 mg zinc monoglycerolate/kg bw/day (corresponding with 13.3 mg Zn^{2+}/kg bw/day and 16.6 mg ZnO/kg bw/d) 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 ZnO, so it is assumed that the effects are due to Zn^{2+},
- the backgound 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 exposure (100-200 d/year), chronic exposure is assumed for risk characterisation.

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

Table B.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 repeated dose toxicity.

European Commission

EUR 21171 EN **European Union Risk Assessment Report**
Zinc oxide, Volume 43

Editors: S.J. Munn, R. Allanou, K. Aschberger, F. Berthault, J. de Bruijn, C. Musset, S. Pakalin, A. Paya-Perez, G. Pellegrini, B. Schwarz-Schulz, S. Vegro.

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Environment and quality of life series

The report provides the comprehensive risk assessment part of the substance zinc oxide. 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.

Part II – Human Health

This part of the evaluation considers the emissions and the resulting exposure to human populations in all life cycle steps. 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 oxide concludes that there is concern for workers. For consumers and humans exposed via the environment the risk assessment concludes that risks are not expected.

The conclusions of this report will lead to risk reduction measures to be proposed by the Commission's committee on risk reduction strategies set up in support of Council Regulation (EEC) N. 793/93.

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