English translation of original German text provided by Janssen PMP, Turnhoutseweg 30, B-2340 Beerse, Belgium.

DERIVATION OF A TOLERABLE EXPOSURE CONCENTRATION FOR SODIUM PYRITHIONE FOR THE AVOIDANCE OF DEVELOPMENTAL TOXICITY EFFECTS AT THE WORKPLACE

By order of:

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1 BACKGROUND AND PURPOSE

Sodium pyrithione (NP) is used as a fungicide in cooling lubricant concentrates, with a concentration of 0.1 to 0.5 percent by weight; this concentration is a maximum of 500 ppm in ready-for-use water-mixed cooling lubricants.

A "maximum allowable workplace concentration" (OELV, or Occupational Exposure Limit Value) of 1 mg/m^3 was already available from the DFG in 1994 (Greim, 1994), in conjunction at the time with the "H" identifier and the pregnancy group "C" *("an embryotoxic effect need not be feared if the OELV value of …. is complied with").*

This OELV value was reviewed in 2012, and its inclusion into the TRGS 900 was proposed. The concentration level of 1 mg/m^3, and the "H" identifier remained unchanged, but the pregnancy group was changed to "Group B" (Hartwig, 2012), and adopted in this form in TRGS 900 as Occupational Exposure Limit (OEL) (with analogous pregnancy group "Z") (AGS, 2012). The identifier "Z" is assigned to substances for which a risk of embryotoxicity cannot be excluded, even in the case of compliance with the OEL. The change in the pregnancy group was required because the NOAEC (**N**on **O**bserved **A**dverse **E**ffect **C**oncentration) for the developmental toxicity effects did not exceed the Occupational Exposure Limit by a factor > 10 (requirement of the OEL concept; see Committee on Hazardous Substances (2010)).

If the pregnancy group "Z" is assigned, however, there is concern that, if pregnant women are employed, developmental toxicity effects, or such effects that should be considered from the perspective of maternity protection, could still be observed, even in the case of compliance with the OEL. Such potential effects are to be reviewed in the context of a risk assessment according to the Hazardous Substances Regulation, and the appropriate protection of vulnerable groups must be ensured.

The present expert opinion carries out a risk assessment of this precisely nature: a concentration will be determined that could occur when handling cooling lubricants under unfavorable conditions. This will be compared to an air concentration that is still considered to be safe from the perspective of developmental toxicity and maternity protection. Due to the indication of skin absorption ("H" marking) in this case, it will also be ensured that the total amounts of sodium pyrithione absorbed in the event of contact with the skin will not be critical.

2 SUBSTANCE IDENTITY

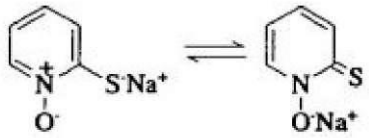
Chemical name:

Sodium pyrithione (NP), 2-Pyridinethiol, 1-oxide, sodium salt, 2-sodium sulfide pyridine-N-oxide, 1-Hydroxy-2(1H)-pyridinethione, sodium salt;

Trade names: Natriumomadin®, Sodium Omadine®, Natrium-Pyrion® CAS No.

3811-73-2; CAS No. 15922-78-8

Structural formula:



There is a balance between the thiol-thione tautomerism.

3 METHODOLOGY

In the present case, it is important to review the available data on the developmental toxicity of sodium pyrithione, and to specify a safe exposure level for pregnant women, at which there is no risk for either the unborn child or the mother.

A "no observed adverse effect concentration" (NOAEC) value should first be established, or in other words, a concentration without any observed negative effects on health. The determination of the NOAEC takes place after careful consideration of all available data from animal studies or from human findings.

Only data relating to animal studies are available for sodium pyrithione, and, for developmental toxicity, only those where absorption took place via the dermal or oral path. An assessment is therefore required with regard to

1. how an orally or dermally absorbed dose compares with an inhaled dose,
2. how a dose administered to an animal can be converted into a human equivalent.

Methodological details on the procedure can be found in the OEL concept (Committee on Hazardous Substances, 2010). When specifying an effective body dose in the laboratory animal, the different basal metabolism between animals and humans must be taken into account, which is done by using the relevant factor ("allometric scaling", in the case of a rat: factor 4). Time extrapolation is not required, insofar as the animals were exposed during the critical days of gestation. The conversion to equivalent human air concentrations takes place under the assumption of an exposure of 8 hours a day and light activity (respiratory volume of 10 m^3 per day). A path-to-path extrapolation (oral or dermal inhalation) can only take place if no path-specific properties have to be considered (e.g., reabsorption differences, "first path" effects, etc.), or these will have to be incorporated in the assessment. In calculating the NOAEC, it is not necessary to include a variability factor according to the Occupational Exposure Limit, because the "safety margin" of 10 (as default value) already provides an appropriate safety margin. Moreover, test results are available from a scenario with a sensitive exposure group, so that the usual variability factor of 5 is not required here. As (pregnant) women are to be considered in the present case, the assumption of the body weight is reduced to 60 kg, instead of the standard assumption of a 70 kg body weight.

4 TOXICOKINETIC DATA

Path-specific kinetic data is of interest in the present context, and is helpful in carrying out the path-to-path extrapolation. Due to its relatively good reabsorption through the skin, NP has been given the suffix “H" . Closer attention must correspondingly be paid to absorption through the skin:

human studies on volunteers in which 10 µg NP in (aquaphor) crème was applied to the skin showed excretion rates in the urine (7 days of urine collection, application area only washed after 24 hours) of 38 %, whereas, with a dermal application of 14 µg sodium pyrithione in acetone, only 5.5 % of the dosage was excreted in the urine (no further data available, cited as Olin 1978 in Hartwig, 2012). As human skin is less permeable than that of rats, the authors of the OELV justification assume that a 100% reabsorption can be assumed for the application of NP in aquaphor crème to rats. As support, the authors state that, in the work cited as Olin 1980, mortality in the mother animals and significant skeletal changes in the offspring were determined after the dermal exposure of rats to NP in aquaphor crème. This indicates a high degree of dermal reabsorption. The dermal absorption is strongly dependent on the vehicle used, however.

A 50% dermal reabsorption is assumed for humans in the current case of cooling lubricants.

As there is no evidence of a "first path" effect in the liver, a path-to-path extrapolation is justified. There is, however, evidence of an enterohepatic circulation of NP (ACP, 2003).

5 JUSTIFICATION FOR THE OEL (2012)

The basis of the applicable OEL is an unpublished study by Olin in 1989 (Greim, 1994, cited as Olin 1989 c). In this study, rats (15 animals per sex and dosage) were exposed to doses of 0.46, 1.1, and 3.8 mg NP /m^3 (in the first 6 weeks) and 8.1 mg NP /m^3 (remaining 7 weeks) for a total of 13 weeks. The exposure took place 6 hours/day for 5 days/week. Four animals from the high dosage group indicated hind leg weakness and a degeneration of the skeletal muscle fibers at the end of the treatment. In addition, the urine volumes were significantly increased in the highest dosage group, and body weight was significantly reduced. The NOAEC of the study is defined at 1.1 mg/m^3.

On the basis of this NOAEC value, the OELV of 1 mg/m^3 was established in 1994 (Greim, 1994). This value was confirmed in both 2001 and 2012 (Greim, 2001; Hartwig, 2012). In 2001, it was determined that the OELV of 1 mg/m^3 for NP in the form of dust relates to an inhalable fraction (labeled “E”).

The OELV at the level of 1 mg/m^3 was adopted as the OEL (TRGS 900).

In TRGS 900, sodium pyrithione is identified with “H", which indicates the relevance of the dermal absorption.

The occupational exposure limits of other countries (Australia, Denmark, Switzerland) for NP are also 1 mg/m^3 (IFA, 2013). An SCOEL value (*Scientific Committee on Occupational Exposure Limits*) is not available.

No OEL value is available for the zinc pyrithione (CAS No. 13463-41-7), which is very similar to NP (Hartwig, 2012). It is stated that the reason for this is that NOAEC values have only been determined for heavily diluted zinc pyrithione suspensions, and that this does not provide any scientific basis for the derivation of an OEL value. Zinc pyrithione is therefore listed in Section IIb of the OEL and BWT (biological workplace tolerance) value lists. As no OEL value has been derived, there is also no allocation to a pregnancy group according to the justification for zinc pyrithione.

DEVELOPMENTAL TOXICITY

6.1 HUMAN DATA

No data is available.

6.2 DATA FROM ANIMAL EXPERIMENTS

6.2.1 INHALATION EXPOSURE

No data is available on NP.

6.2.2 ORAL EXPOSURE

The development toxicity studies that are currently available on oral exposure to NP are all unpublished. The studies are therefore quoted in this report according to the OEL justification quoted.

In a two-generation study, Olin (cited as Olin 1989 a in Greim, 1994) orally exposed 25 male and 25 female rats (by gavage) to 0.5, 1.5 and 3.5 mg NP/kg x d, starting 77 days before mating. The female animals were exposed up to 25 days after the birth of their offspring. In the F1 generation, the exposure of both sexes started 98 days before mating, and lasted up to 21 days after the birth of the offspring for female animals. At 1.5 mg/kg x d, the number of sarcolemmal nuclei and accumulations of fat in the muscle fibers increased in 3/25 female animals of the F1 generation. Muscular atrophy of the upper hind limbs was also observed. At 3.5 mg/kg x d, mating behavior and fertility were impaired in male animals of the F0 generation. In both generations, however, neither the duration of the gestation period, the size of the litter nor the reproductive organs were found to be changed, although a dose-dependent muscular atrophy of the upper hind limbs was observed. The F2 generation did not show any abnormalities; no data on this is available with regard to the F1 generation. The NOEL of the study can be defined as 0.5 mg/kg x d. The $NOAEL_{dev}$ is 3.5 mg/kg x d in this study.

Further research by Olin (cited as Olin 1972 b in Greim, 1994) suggests an embryotoxic potential of NP. Female rats were exposed to 0, 7.5 and 15 mg/kg x d in the form of an aqueous solution (also administered by gavage) from gestation day 6 to 15. With simultaneous maternal toxicity (body weight loss), embryotoxic effects in the form of bifurcated, shortened, missing or fused ribs and/or deformed or fused sternum sections were observed in both dosage groups. This study is probably the same study that was quoted in the 2012 OEL justification under bibliographical reference "Olin 1976".

Another older study by Olin (cited as 1969a in Greim, 1994) supports the finding of embryotoxicity in rats, although at much higher exposure doses (50 mg/kg x d) and with dubious maternal toxicity.

One of the studies cited in the 2012 OEL justification (Hartwig, 2012, here also cited as Olin 1976) describes a (gavage) exposure of 20 female rats during gestation (days 6-15) of 0, 0.3, 1.0, 3.0 and 7.5 mg NP/kg x d. No data was provided on maternal toxicity, and rib deformity (curved ribs) was not observed from a clearly dose-dependent viewpoint. In the OEL justification, it was argued that the slightly increased incidence of rib deformity at 0.3 mg/kg x d (1.2 %) could not be clearly interpreted as a substance-specific effect, since data on historical checks, in particular, is missing. It could therefore also relate to a spontaneous finding. 2.2 % deformity in ribs was observed in the highest dosage group. This study can therefore only be used as supportive documentation.

Developmental toxicity studies in rats and rabbits are also available for zinc pyrithione (Nolen and Dierckman, 1979) (SCCNFP, 2002) and (Olin 1992 cited by Hartwig, 2012). The lowest $LOAEL_{dev}$ reported in these studies is at 1.5 mg/kg x d in rabbits (Olin 1992 cited by Hartwig, 2012). In this case, an increased number of reabsorptions and post-implantation losses, a decreased number of living fetuses and complete reabsorption (1/20) were observed. In the mother animals, the body weight and the uterine weight gain were found to be reduced at the same dose. The $NOAEL_{mat}$ and the $NOAEL_{dev}$ are at 0.5 mg/kg x d. In rats, the lowest $NOAEL_{dev}$ in these studies was found at 3 mg/kg x d (Olin 1992 cited by

Hartwig, 2012). The effects observed in the fetuses at this dose were fused ribs (3 fetuses/2 litters). Both the $NOAEL_{mat}$ and the $NOAEL_{dev}$ are at 0.75 mg/kg x d. Maternal toxicity (reduced body weight gain, increased salivation) was also observed at 3 mg/kg x d. Other studies report significantly higher $NOAEL_{dev}$ values (5 mg/kg x d in rabbits, 7.5 mg/kg x d in rats).

6.2.3 DERMAL EXPOSURE

Olin (cited as Olin 1980 in Greim, 1994) dermally exposed pregnant rats to 0, 0.5, 1.5, 3 and 7 mg NP/kg x d using aquaphor crème as carrier material. The exposure took place from gestation days 6 to 15, and the animals were examined on gestation day 20. At 7 mg/kg x d, maternal toxicity (reduced body weight gain) and mortality (5/25) were found with simultaneous embryonic toxicity in the form of deformed ribs, and extremities. The authors assessed this effect to be secondary due to the marked maternal toxicity. The NOAEL for embryo-toxic effects is 3 mg/kg x d.
In a prenatal developmental study in rabbits, no effects on the fetus were found at doses up to 5 mg/kg x d (0, 1.0, 2.5 and 5 mg/kg x d)(cited as Olin 1987 j in Greim, 1994). The $NOAEL_{dev}$ in rabbits is therefore > 5 mg/kg x d.

A study of female pigs (four animals per dose group) with 10, 30 and 100 mg / kg x d and epicutaneous exposure led to no conception of the mother animals in the highest dose group. No reproductive or embryotoxic effects were observed in the medium and low dose groups, apart from a reduced conception.

Dermal studies of the developmental toxicity of zinc pyrithione are available for rats, rabbits and pigs (e.g. Nolen and Dierckman, 1979). All reported LOAEL values lie above the values reported for NP.

6.2.4 SUMMARY

After oral administration, skeletal variations in fetuses (forked, shorter, missing or fused ribs, fused or deformed sternum sections) were found in rats at doses of 7.5 mg/kg x d). The NOAEL for developmental toxicity in rats following oral exposure is > 3.5 mg/kg x d, the highest concentration tested in this study.

After dermal exposure, decreased fetal weights, as well as skeletal changes (ribs, extremities), were observed in rats at 7 mg/kg x d. The NOEL of the developmental toxicity after dermal exposure can be defined as 3 mg/kg x d.

The OELV justification from 2012 indicates that the skeletal changes in fetuses are considered to be an effect that was relevant for the evaluation, as these occurred with different exposure routes and comparable effects also occurred after exposure to zinc pyrithione. These effects are therefore not interpreted as a non-specific consequence of the maternal toxicity.

The developmental toxic effects that were observed after exposure to zinc pyrithione correspond to the effects that are caused by NP (ribs changes in the fetuses). The fact that, in some studies, zinc pyrithione was already showing effects at lower doses ($NOAEL_{mat}$, $NOAEL_{dev}$: 0.5 mg/kg x d and 0.75 mg/kg x d) after oral exposure is possibly due to a slightly higher potency of the substance: zinc pyrithione is more toxic than NP. A comparison of the lethal doses (LD_{50}) supports this assumption (zinc pyrithione LD_{50} (4 h) inhalation, rat: 140 mg/m^3 for whole body exposure, 610 mg/m^3 for head-nose exposure, LD_{50} oral, rat 92-266 mg/kg body weight, mouse 160-1000 mg/kg body weight, NP LD_{50} (4 h) inhalation, rat: 800-1300 mg/m^3 LD_{50} oral, rat and mouse 1000 to 2000 mg/kg body weight).

Hitherto, it has been unclear whether the effects observed in fetuses (skeletal changes) are due to the neurotoxic effects of NP. It is conceivable that skeletal malformations were caused by muscular atrophy (Hartwig, 2012).

7

According to expert testimony, a maximum concentration of 0.05% NP (500 ppm) is expected in the use of NP in water-mixed cooling lubricants.
Safety Data Sheets for the concentrate data are available on the Internet, however, that indicate concentrations of < 1% in the concentrate. This is, however, a vague upper limit, which could be specified through a manufacturer survey within the context of this project and be limited more accurately to < 0.5%. With dilution (concentration: water-mixed cooling lubricant = 1:10), the above-mentioned 0.05% is obtained.

7.1 INITIAL EXPOSURE ESTIMATE (INHALATION)

Due to the low volatility, we assume that there is proportionately the same amount of NP in the air as in the liquid. We also assume that the air benchmark value of 10 mg cooling lubricant/m^3 is maintained. This value is actually intended for cooling lubricants present as a gas and as an aerosol (Breuer, 1997; Breuer and Pfeiffer, 1989; Kiechle et al, 1997.) At this point, and adopting a "worst case" scenario, we assume that the entire 10 mg/m^3 is present as an aerosol, and that a proportion of 500 ppm is present in aerosol form as NP. This results in an exposure level of < 5 µg NP/m^3.

In principle, there is a presumption of an inhalation exposure, however, in the case of a substance such as NP, which can also be well absorbed dermally (assuming 50% dermal reabsorption, see also Section 4), absorption through the skin will also be considered (see the following section).

7.2 INITIAL EXPOSURE ESTIMATE (DERMAL)

For an initial assessment of dermal exposure, the RiskofDerm model was used (Warren et al., 2006), which was used in a version implemented in MS Excel®. The following input parameters were set up:

- Dermal Exposure Operation (DEO) unit 6: "mechanical treatment", as the use of cooling lubricants is specifically mentioned here.
- Condition of the aggregate: liquid, as cooling lubricant is explicitly mentioned in the model, even if a solid object is being processed.
- Duration: 214 minutes, this represents the upper limit of the validity range in this DEO unit; this is likely to represent a "worst case", however, for Scenario 2 (see below).
- NP concentration in ready-to-use cooling lubricant: 0,05 %
- Density of the cooling lubricant: 1 mg/µl; Riskofderm expresses the exposure in µL that was converted with a density of 1 in mg.

In addition, a distinction is made between two scenarios:

- Scenario 1 assumes a greater distance from the processed object (for example, when turning), but a frequent/constant contact with the cooling lubricant.

- Scenario 2, on the other hand, assumes a closer proximity to the processed object, but occasional/irregular contact (for example, when setting up). The total duration of 214 minutes was maintained, even if this activity is performed less frequently than that of the first scenario. In view of the result, this is the more critical scenario, due to the fact of being closer to the product (cooling lubricant)!

The result provided by the model, and also converted here with regard to the cooling lubricant components, represents the potential dermal exposure (i.e. without taking account of protective equipment).

It refers, unfortunately, only the exposure of the body without hands. This is due to the fact that RiskofDerm generally makes a differentiation between the exposure of the hands and of the (rest of the) body, but does not have sufficient qualified data to estimate the exposure of the hands for the model that is relevant here (DEO unit 6).

For both scenarios, a potential dermal exposure to NP of 6.1 or 9.7 mg/d results in the 90th percentile. The corresponding 75th percentiles, which allow a more realistic view in the consideration of the exposure via different paths, are lower by a factor of 2.6 in both scenarios. The varied input parameters and the results of the exposure assessment are presented together in the following.

Scenario 1

Parameter	Value	Justification		
Separation	> 1 arm length	Typically during lathe work?		
Frequency of contact	Frequent / constantly	Used as the “worst case”		
Exposure assessment		**Median**	**75th percentile**	**90thpercentile**
Dermal exposure (cooling lubricant)	mg/d	1.980	5.790	15.200
Dermal exposure (NP)	mg/d	0.99	2.9	7.6

Scenario 2

Parameter	Value	Justification		
Separation	< 1 arm length	Used as the “worst case”		
Frequency of contact	Rare/irregular	Derived from the work of setting-up operations		
Exposure assessment		**Median**	**75th percentile**	**90th percentile**
Dermal exposure (cooling lubricant)	mg/d	3.170	9.275	24.300
Dermal exposure (NP)	mg/d	1.6	**4.6**	12.2

Two considerations will be discussed In the following calculation:

a) Can the total body exposure without hands be equated with an exposure of essentially only the hands (as explained above)?

b) Ultimately, should the 75th percentile or the 90th percentile be used in the respective scenario?

With regard to a) the exposures estimated above for the cooling lubricant itself (15,200 and 24,300 mg in the 90th percentile) are approximately in the range of 90th percentiles that were mentioned in a recent review article for the exposure of the hands and forearms with coolant lubricant applications (12,000 - 36,000 mg). In this case, the lower end of the range is also likely to include data from studies in which gloves were worn (Cherrie and Semple, 2010). The exposure areas "total body exposure

without hands" (used) and exposure of hands and forearms (no better data for modeling) correspond approximately.
Our transfer is therefore justified. Data other than the 90th percentile is not available in the work of Cherrie and Semple.

With regard to b), the upper end of this range (36,000 mg) in Cherrie and Semple (2010) should apply for both hands: for the usually assumed surface area of 840 cm^2, however, this results in an exposure of (36,000 mg/840 cm^2 =) 43 mg/cm^2, which is significantly higher than the range of 12 mg/cm^2 that has just been considered as realistic (EC, 2003). For this reason, and because the other assumptions have been mainly calculated under "reasonable worst case" conditions, we see the 75th percentile as being sufficiently conservative as the comparison value (4.6 mg NP/d).

To summarize, a dermal exposure of **4.6 mg NP / d** (Scenario 2 for body with long duration; highlighted by yellow shading in the table) therefore appears to also represent a conservative estimate for exposure of the hands plus the (rest of the) body.

8 EXTRAPOLATION OF A TOLERABLE CONCENTRATION

A detailed presentation of the relevant developmental toxicity studies is carried out in Section 6.

The two NOAEL values for developmental toxicity in rats are > 3.5 mg/kg x d (oral exposure) (cited as Olin 1989 a in Greim, 1994) or 3.0 mg/kg x d (dermal exposure) (cited as Olin 1980 in Greim, 1994).
The NOAEL of 3.0 mg/kg x d after dermal exposure is used as a basis to calculate a human equivalent air concentration at the workplace. Division by a factor of 4 (for allometric scaling from the rat to humans) results in a human equivalent dose of:

0.75 mg/kg body weight x d.

Assuming a 60 kg body weight (for the reason given in Section 3), a total dose of 45 mg/d can be calculated.

8.1 CONVERSION TO A 100% INHALATION EXPOSURE

Because a 100% dermal reabsorption, as well as 10 m^3 respiratory volume per working day is assumed, a human equivalent air concentration at the workplace to the level of 45 mg/d / 10 m^3/d = 4.5 mg/m^3 can be calculated.
The NOAECd_{ev} value of 5.25 mg/m^3 calculated in the OELV justification (Hartwig, 2012) is also calculated from the NOAEL for developmental toxicity of 3 mg/kg x d (dermal exposure of rats). The only difference from the calculation shown here is the default assumption of 70 kg body weight in the OELV justification as opposed to 60 kg (this report).
If the maternal toxicity that has been observed in developmental toxicity studies was to be used as the basis of this calculation, a NOAEL of 0.5 mg/kg x d would be assessed. This is described by Olin 1989 a (cited according to Greim, 1994) in an oral, two-generation study. The LOAEL for maternal effects in this case is 1.5 mg/kg x d (including muscular atrophy of the upper hind limbs). A conversion into human equivalent air concentrations results in a NOAEC of 0.75 mg/m^3.

As already mentioned, a 10-fold separation between the exposure and the NOAEC$_{dev}$ is required in order to be able to assign the pregnancy category "Y" according to the OEL concept. From this, the immediate result is:

NOAEC = 4.5 mg/m^3 divided by 10: "Safe air concentration taking the developmental toxicity into account" < 0.45 mg/m^3 (assuming 100% exposure via inhalation; no absorption of the substance through the skin).

8.2 TAKING ACCOUNT OF A PROPORTIONATE PERCUTANEOUS EXPOSURE

As shown in Section 7.2, a percutaneous absorption of NP must also be considered in addition to the inhalation exposure. A dermal exposure of 4.6 mg/d (Scenario 2 for body with long duration; 75th percentile) will be accepted. Assuming 50% dermal reabsorption, this is equivalent to 2.3 mg/d. This dermally absorbed amount corresponds to a maximum air concentration of 0.23 mg/m^3 (= 2.3 mg/10 m^3) (just as much would be taken up by exposure to 230 µg/m^3 (inhalation), as it corresponds to the exposure/day through the skin).

Taking the dermal exposure of women into account, this therefore results in a tolerable exposure to air with a value of

0.45 mg/m^3 – 0.23 mg/m^3 = 0.22 mg/m^{3}From

this, the result is:

Orientation value for NP,
which also protects against developmental toxicity damage and in which a relevant absorption of NP through skin contact is taken into account (rounded): **0.2 mg/m^3**

9 DISCUSSION AND CONCLUSIONS

This paper is concerned with the developmental toxic effects of NP. Starting from an NOAEL of 3 mg/kg x d for developmental toxicity effects in rats after dermal exposure, a human equivalent air concentration of 4.5 mg/m^3 can be calculated. The suggestion of a dermal reabsorption of 100% in animal experiments therefore seems not to be conservative (lower effective dose at lower percutaneous absorption), but rather justified, because the value is the same level as after oral exposure (oral: $NOAEL_{dev}$ = 3.5 mg/kg x d , dermal: $NOAEL_{dev}$ = 3 mg/kg x d); the adoption of a lower reabsorption would lead to a higher systemic toxicity after dermal absorption compared to oral gavage exposure at about the same external exposure levels. There is no indication of this.

The possible enterohepatic circulation after oral intake also does not seem to impact greatly on the path-to-path comparison. Maternal paralysis effects after oral exposure in rats are of the same order of magnitude as the same effects by inhalation: (see Section 6.2.2): $LOAEC_{from\ oral}$ = 1.5 mg/kg x d / 4 = 0.6 mg/kg x d x 60/10 = 3.6 mg/m^3; $NOAEC_{from\ oral}$ = 1.2 mg/m^3. There is therefore no evidence to suggest that a path-to-path extrapolation (oral → inhalation) should not be permitted.

The following uncertainties must be observed, however:

- The assessment of skeletal changes as adverse is a conservative rating. It is possible that these effects only occur secondarily to maternal toxicity, and the described changes cannot be definitely classified as disadvantageous (adverse).
- An insight into the original work on developmental toxicity was not possible, as all the works are unpublished.

- The dermal reabsorption of NP in humans is assumed to be 50%. Corresponding quantifications are not assured, but are cautious.
- A scenario from RiskofDerm was adopted for the proportional skin exposure, which can only estimate the approximate skin exposure, but which is again a cautiously laid-out scenario.
- The air concentration estimated above is not confirmed by measurements, but was estimated through the assumption: “Same concentration in the aerosol as in the water-mixed cooling lubricant”. It is therefore a rough estimate, which nevertheless appears cautious. It would be advisable to secure the resulting indoor air concentration through measurements.
- The above-mentioned concentrations of NP in the water mixed cooling lubricant were stated by the vendor, but were accepted here without any testing.

With these limitations, a clear picture emerges:

The air concentration, which also protects against developmental toxicity damage, whereby a relevant absorption of NP through skin contact is taken into account, lies at 0.2.mg/m^3.

The expected air concentration based on the exposure estimation is around 5 µg/m3.

A “margin of safety” (MoS) of approx. 40 (200 µg/m^3 to 5 µg/m^3) is the result. In the use of sodium pyrithione in metalworking lubricants, it is not expected that there will be developmental toxicity or maternal toxicity effects for pregnant women.

The assignment of a pregnancy group "Z" in the TRGS 900 has no restrictive meaning for the exposure scenario being tested here.

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For sodium pyrithione (CAS Number: 3811-73-2, 15922-78-8), there is an occupational exposure limit (OEL) according to TRGS 900 at the level of 1 mg/m^3. Additional indications are a mark "H" (indication of the risk of percutaneous absorption) and "Z" (a reference to a developmental toxic potential that cannot be excluded, and that could still be relevant while maintaining the OEL).

Sodium pyrithione can be mixed with water, and is therefore used as a fungicide in water-mixed cooling lubricants (KSS). As women could also be exposed to cooling lubricants at the workplace through the air (inhalation of aerosols) and through skin contact (aerosol deposition and direct contact with contaminated work pieces or wetting/splashing of the skin with cooling lubricants), a risk assessment was to be carried out to determine the air concentration at which the safe handling of cooling lubricants containing sodium pyrithione is possible.

Analogous to the approach of the OELV Commission, an animal study with dermal exposure was used to assess developmental toxicity and maternal toxicity. The corresponding dose with no adverse health effects is 3 mg/kg body weight and day. This dose can be converted into an air concentration of 4.5 mg/m^3 (NOAEC). An air concentration that is lower by a factor of 10 than this reported NOAEC is "safe" (according to the possibility of assigning the pregnancy group "Y"). A safe concentration of 450 µg/m^3 therefore results, if it is assumed that there is no skin contact with the substance.

Realistically, however, in light of the "H" mark and exposure conditions at the cooling lubricant workplace, it must be considered that relevant skin contact can also occur with the cooling lubricant. A dose that could be absorbed through the skin during the working day is therefore calculated using modeling. This dose has been taken into account to correct (to reduce) the tolerable value via air intake.

The air concentration, which also protects against developmental toxicity damage, whereby a relevant absorption of NP through skin contact is taken into account, is 0.2 mg/m^3 (200 µg/m^3). Given the usual (and conservatively estimated upper) content of sodium pyrithione in cooling lubricant concentrates and water-mixed cooling lubricants, a maximum expected air concentration at the cooling lubricant workplace was also calculated. This is approx. 5 µg/m^3. It would be appreciated if this conservative, but only roughly predictable air concentration could be secured through measurement readings.

A “margin of safety” (MoS) of approx. 40 (200 µg/m^3 to 5 µg/m^3) is the result. With regard to the use of sodium pyrithione in cooling lubricants, it is therefore not expected that there will be developmental toxicity effects or maternal toxicity effects for pregnant women.

The assignment of a pregnancy group "Z" in the TRGS 900 has no restrictive meaning for the exposure scenario being tested here.

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