The MAK Collection for Occupational Health and Safety

GMS PUBLISSO ZB MED-Publikationsportal Lebenswissenschaften

Sodium pyrithione

MAK Value Documentation, supplement – Translation of the German version from 2019

A. Hartwig[1,*] MAK Commission[2,*]

1 *Chair of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Institute of Applied Biosciences, Department of Food Chemistry and Toxicology, Karlsruhe Institute of Technology (KIT), Adenauerring 20a, Building 50.41, 76131 Karlsruhe, Germany*

2 *Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Kennedyallee 40, 53175 Bonn, Germany*

* *email: A. Hartwig (andrea.hartwig@kit.edu), MAK Commission (arbeitsstoffkommission@dfg.de)*

Keywords

sodium pyrithione; neurotoxicity; paralysis; MAK value; maximum workplace concentration; peak limitation; developmental toxicity; skin absorption

Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated sodium pyrithione [3811-73-2; 15922-78-8] considering all toxicological end points. Available publications and unpublished study reports are described in detail. Sodium pyrithione is neurotoxic in rats and rabbits, but not in monkeys. As there is no sufficient mechanistic explanation for the observed differences between the species, the rat as the most sensitive species is used for the derivation of a maximum concentration at the workplace (MAK value). The NOAEC in a 90-day inhalation study with rats is 1.1 mg/m^3. In a chronic feeding study with rats, a NAEL of 0.16 mg/kg body weight and day is derived from the LOAEL of 0.5 mg/kg body weight and day. Both the NOAEC and the NAEL correspond to a MAK value of 0.2 mg/m^3 for the inhalable fraction. As a systemic effect is critical, the substance remains classified in Peak Limitation Category II. As the initial half-life of sodium pyrithione is in the range of up to 2.8 hours, an excursion factor of 2 is assigned. In developmental toxicity studies, the most critical effects of sodium pyrithione are skeletal anomalies in rats. NOAELs for developmental effects are 2 mg/kg body weight and day after oral treatment of rats as well as 3 and 5 mg/kg body weight and day after dermal application to rats and rabbits, respectively. The differences between the NOAELs for rats and rabbits scaled to an inhalation concentration at the workplace and the MAK value are considered sufficient. Therefore, damage to the embryo or foetus is unlikely when the MAK value is not exceeded and sodium pyrithione is assigned to Pregnancy Risk Group C. Sodium pyrithione is still regarded as a non-genotoxic and non-carcinogenic substance. Skin contact may contribute significantly to systemic toxicity and sodium pyrithione remains designated with an "H" notation. Sensitization is not expected based on the limited data available.

Citation Note:
Hartwig A, MAK Commission. Sodium pyrithione. MAK Value Documentation, supplement – Translation of the German version from 2019. MAK Collect Occup Health Saf. 2023 Mar;8(1):Doc016. https://doi.org/10.34865/mb381173kske8_1ad

Manuscript completed:
21 Mar 2018

Publication date:
30 Mar 2023

MAK value (2018)	**0.2 mg/m³ I (inhalable fraction)**
Peak limitation (2001)	**Category II, excursion factor 2**
Absorption through the skin (1994)	**H**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (2018)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value	**–**
CAS number	3811-73-2; 15922-78-8
Melting point	250 °C (decomposes) (ECHA 2016)
Vapour pressure at 25 °C	0.00000046 hPa (ECHA 2016)
log K_{OW}	0.002 (ECHA 2016)
Solubility	646.6 g/l water at 20 °C (ECHA 2016)

Documentation for sodium pyrithione was published in 1994 (Greim 1998), followed by a supplement on peak limitation in 2001 (Greim 2001, available in German only) and a supplement on prenatal toxicity in 2012 (Hartwig 2012 a, available in German only).

In 2016, the Commission began using a revised approach for assessing substances with a MAK value based on systemic effects and derived from inhalation studies in animals or studies with volunteers at rest; this new approach takes into account that the respiratory volume at the workplace is higher than under experimental conditions (see List of MAK and BAT Values, Sections I b and I c). This supplement evaluates whether the MAK value for sodium pyrithione needs to be re-assessed as a result of the higher respiratory volume at the workplace.

1 Toxic Effects and Mode of Action

A typical sign of toxicity in rats and rabbits after single or multiple applications of sodium pyrithione is reversible paralysis of the hind extremities. This effect is not observed in monkeys and dogs. In a 2-year study, degenerative changes in the nerves and skeletal muscles were observed in rats given oral sodium pyrithione doses of 0.5 mg/kg body weight and day and above.

Sodium pyrithione causes irritation of the skin and eyes in rabbits.

There is only little positive evidence that sodium pyrithione induces contact sensitizing effects in humans. Studies in guinea pigs yielded negative findings. There are no clinical findings that indicate photocontact sensitizing effects in humans and the findings obtained under experimental conditions are unclear.

In a 2-generation study in SD rats, sodium pyrithione impaired fertility and mating behaviour in male F0 animals at a dose of 3.5 mg/kg body weight and day. In a developmental toxicity study in rats, reduced mean body weights, an increased percentage of small foetuses and incomplete ossification of sternal segments, metacarpal and metatarsal bones were observed in the foetuses after oral exposure to doses of 4 mg/kg body weight and day and above. In a developmental toxicity study in the same species with dermal application of 7 mg/kg body weight and day, decreased body weights and reduced ossification of ribs and extremities were observed in the foetuses. No adverse effects on

development were observed in New Zealand White rabbits after dermal application of doses up to 5 mg/kg body weight and day.

Sodium pyrithione was not found to cause genotoxic effects in Salmonella mutagenicity tests, in HPRT tests, or in the UDS test in rat hepatocytes. However, only low concentrations were tested because of the cytotoxicity of the compound. Sodium pyrithione significantly increased the incidence of aberrations without gaps in an in vitro chromosomal aberration test with and without metabolic activation. The substance did not cause any effects in 2 micronucleus tests in vivo.

Sodium pyrithione did not induce carcinogenic effects after dermal application in mice or in 2 studies after oral exposure of rats.

2 Mechanism of Action

Sodium pyrithione may induce neurotoxicity by causing an influx of calcium into the neurons as was observed in vitro. This increased concentration of intracellular calcium impairs the integrity of axonal microtubules in rodents, which may explain the neurotoxic findings in vivo. The primary metabolite of sodium pyrithione in serum, 2-methylsulfonyl pyridine, which does not induce neurotoxicity in rats, did not lead to an increased influx of calcium into the neurons in studies in vitro (Knox et al. 2008).

The neurotoxicity induced by sodium pyrithione in rats and rabbits is not observed in monkeys and dogs (see Section 5.2.2). In studies in vitro in isolated foetal motor neurons of rats and rhesus monkeys (Macaca mulatta), exposure to sodium pyrithione led to a concentration-dependent increase in intracellular calcium levels in both species. However, the EC_{50} levels in rat neurons were about 33 times lower than the levels in monkey neurons. The authors suggested that the higher threshold concentration and the higher EC_{50} levels in monkeys may explain why, unlike in rats, neurotoxic effects were not observed in monkeys (Knox et al. 2008).

Tetrodotoxin, nifedipine and ouabain, which are blockers of voltage-dependent Na^+ and Ca^{2+} channels and of Na^+/K^+-ATPase, did not influence the effects of sodium pyrithione in rat neurons. By contrast, SKF 96365, a non-specific antagonist of certain store-operated calcium channels which also blocks TRP channels (transient receptor potential channels), inhibited the induction of calcium influx into the neurons of rats and monkeys by sodium pyrithione (Knox et al. 2008). These in vitro studies suggest that there may be quantitative differences in the effects of sodium pyrithione on the peripheral neurons of rats and monkeys. However, it was not possible to derive potential mechanisms that would explain these considerable interspecies differences. As a result of the high level of agreement with the neuroanatomy and neurophysiology of humans, non-human primates (NHP) are considered a valuable animal model in the neurosciences (Capitanio and Emborg 2008). The considerable quantitative differences between the rodent and the NHP animal model observed in the in vitro and in vivo studies reviewed suggest a higher susceptibility of the rat to peripheral neurotoxic effects induced by sodium pyrithione. However, whether the effects observed in rodents are attributable to a mechanism of action "specific to rats" that is less relevant for humans cannot be determined with certainty.

3 Toxicokinetics and Metabolism

There are no new data available.

There are no data available for absorption by inhalation. Sodium pyrithione is rapidly and almost quantitatively absorbed after oral administration to rats, rabbits and monkeys (Greim 1998).

The half-lives determined for the initial and terminal phases of sodium pyrithione after intravenous injection were 0.7 to 2.8 hours and 27 hours to 6 days, respectively (Greim 1998).

The absorption of sodium pyrithione through the skin largely depends on the solvent used and the concentration applied. After dermal application of radioactively-labelled sodium pyrithione in acetone to the skin of 8 volunteers, 5.5% of the radioactivity was detected in the urine collected over a 7-day period (Greim 1998). In animal studies, up to 8% of the amount applied to the skin was recovered in the faeces and urine (ECHA 2016). About 1 µg/cm^2 was absorbed

after epicutaneous application of 1 mg of sodium pyrithione in shampoo to the skin of rats for 10 minutes (Howes and Black 1975 in Greim 1998). If this value is extrapolated to a standard area of application of 2000 cm^2, the amount absorbed would be 2 mg.

Following the absorption of sodium pyrithione, 2-methylsulfonyl pyridine was the main metabolite found in human and animal plasma. The available studies that investigated the main metabolites in the urine after oral, dermal or intravenous exposure did not find considerable species differences in the metabolism of sodium pyrithione (Greim 1998). Therefore, the quantitative species differences in neurotoxicity cannot be attributed to differences in metabolism.

4 Effects in Humans

No data for single exposures, reproductive toxicity, genotoxicity and carcinogenicity have become available. No new data are available for repeated exposure and effects on the skin and mucous membranes.

Allergenic effects

Sensitizing effects on the skin

On the basis of experience with sodium pyrithione, the substance is known to induce only very weak allergenic effects. Only very few reports assumed that allergic contact eczema was caused by occupational exposure to sodium pyrithione, for example as a component of metal-working fluids (Table 1; see also Greim 1998).

Only relatively few case reports of supposed contact allergic reactions are available for zinc pyrithione, in spite of its widespread use, particularly as an ingredient in anti-dandruff shampoos or formulations (see Hartwig 2012 b).

The 1994 documentation (Greim 1998) included 2 studies that found that sensitization was not induced by sodium pyrithione after repeated application to the skin of volunteers. In another study, phototoxic or photocontact sensitizing effects were not induced by a 2.5% aqueous sodium pyrithione formulation. However, the study did not provide data for the wavelength range used (Greim 1998). In contrast to this, a photomaximization test yielded positive results in 6 of 25 volunteers after the application of 2.5% sodium pyrithione (no other details); however, no other data were provided. The test with zinc pyrithione yielded negative results. According to a protocol published at an earlier time, induction was carried out by 6 occlusive applications of sodium pyrithione for 24 hours over a period of 3 weeks; each application was followed by treatment with UV radiation (simulated sunlight spectrum, 3-fold minimal erythema dose). The challenge treatment with occlusive application for 24 hours followed by UV-A radiation was carried out 14 days later (315–400 nm, 4 J/cm^2) (Kaidbey 1991; Kaidbey and Kligman 1980; Kligman and Kaidbey 1982).

Sensitizing effects on the airways

There are no data available.

Tab. 1 Reports of reactions to sodium pyrithione in epicutaneous tests in patients with suspected contact allergy

Persons tested	Test substance, concentration (vehicle)	Results	Contact/remarks	References
1 metal worker with eczema on the hands	sodium pyrithione, 0.5% (petrolatum)	1+ and 2+ after 48 or 96 hours, respectively	less than 1% sodium pyrithione in the metal-working fluid concentrate	le Coz 2001
1 lathe operator with dermatitis on the back of the hands	sodium pyrithione, 0.1% (water)	1+ and after a second test 3+ (after 48 hours)	metal-working fluid containing 0.1% to 1% sodium pyrithione; questionable reaction to the metal-working fluid used and 2+ response to the metal-working fluid concentrate (5% in buffer solution)	Isaksson 2002
	zinc pyrithione, 1% (petrolatum)	negative		

Tab. 1 *(continued)*

Persons tested	Test substance, concentration (vehicle)	Results	Contact/remarks	References
Results of patch tests in larger collectives:				
40 metal workers with contact dermatitis	sodium pyrithione, 1% (water)	0 of 40 positive	40 workers tested of a total of 286 workers from 10 plants	de Boer et al. 1989
185 metal workers with exposure to metal-working fluids	sodium pyrithione, 0.1% (water)	2 of 185 positive (1+; after 72 hours)	test period: 2002 to 2003	Geier et al. 2004
135 metal workers with exposure to metal-working fluids	sodium pyrithione, 0.1% (water)	1 of 135 positive (after 72 hours)	test period: 6/2004 to 6/2005	Geier et al. 2006
721 metal workers with exposure to metal-working fluids	sodium pyrithione, 0.1% (water)	5 of 721 positive (4 × 1+, 1 × 2+; after 72 hours)	test period: 2005 to 2009; in addition, 13 × questionable and 2 × irritant reactions	Geier et al. 2013
3 patients with dermatitis induced by cosmetics	no data	1 of 3 positive (no other data)	test period: 2010 to 2015; findings listed in table form for a total of 603 patients with dermatitis induced by cosmetics	Goossens 2016
181 metal workers	sodium pyrithione, 0.1% (water)	0 of 181 positive		Gruvberger et al. 2003
1696 patients	sodium pyrithione, 0.1% (water)	5 of 1696 positive	test period: 1990 to 1994; in addition, 12 × questionable or irritant reactions	Schnuch et al. 1998
252 metal workers with exposure to metal-working fluids	sodium pyrithione, 0.1% (water)	4 of 252 positive (after 72 hours)	test period: 1/1990 to 3/1991; no questionable or irritant reactions	Uter et al. 1993

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

The 4-hour LC_{50} in Sprague Dawley rats was determined to be 1300 mg/m^3 in male animals and 800 mg/m^3 in females (Olin 1987 i in Greim 1998).

5.1.2 Oral administration

The LD_{50} for sodium pyrithione in rats and mice was found to be in a range from 1000 to 2000 mg/kg body weight (Moe et al. 1960 in Greim 1998; Olin 1987 b in Greim 1998).

The LD_{50} for sodium pyrithione in female Sprague Dawley rats was 1208 mg/kg body weight. Signs of toxicity were ataxia, bent posture, lethargy, reduced breathing rates and laboured breathing, clonic or tonic seizures, piloerection, ptosis, loss of the righting reflex and splayed gait. The surviving animals recovered within 3 to 8 days. Haemorrhagic lungs, dark or irregularly pale livers, dark kidneys and haemorrhage of the gastric mucosa were observed in the animals that died (Weyl 1996).

5.1.3 Dermal application

After a single dermal application of sodium pyrithione to rabbits, the LD_{50} was 1800 mg/kg body weight (Olin 1987 c in Greim 1998).

An LD_{50} of > 2000 mg/kg body weight was determined for Sprague Dawley rats after semi-occlusive dermal application of sodium pyrithione (moistened solid, purity > 90%) to the shaved dorsal skin for 24 hours. Mortality did not occur. Local irritation was observed at the application site (erythema and scabbing) in addition to chromodacryorrhea (hypersecretion of the Harderian glands), which was reversible at the latest after 10 days. No unusual findings were determined with respect to body weights and at necropsy (Rütgers Organics 2001 b).

5.1.4 Intravenous and intraperitoneal injection

There are no new data available.

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

In a range-finding study, groups of 10 male and 10 female rats were exposed to sodium pyrithione concentrations of 0, 10, 20 or 42 mg/m³ (5 days a week, no other details). Body weight gains were severely reduced after 2 weeks. Weakness of the hind legs was observed in several animals. The study was discontinued after 3 weeks because of high mortality. A second range-finding study with exposure concentrations of 0, 0.042, 0.11, 0.34, 1.12 or 3.03 mg/m³ (5 days a week, no other details) was carried out for 4 weeks. After 3 weeks, weakness of the hind legs was observed in 5 of 10 females of the high concentration group; 1 female of this group died. Body weights were not affected by the treatment in any of the groups. No unusual findings were detected in the microscopic examination of the respiratory tract (Olin 1989 c).

In a 90-day study reviewed in the 1994 documentation (Greim 1998), groups of 15 male and 15 female CD rats were exposed to sodium pyrithione concentrations of 0, 0.46, 1.1 or 3.8 mg/m³ (6 hours a day, 5 days a week, whole-body exposure, equivalent aerodynamic diameter 1.3 µm (GSD 1.95)) in the form of an aerosol of an aqueous solution (0.14%–0.6%). Due to the absence of toxicity, the highest concentration was increased to 8.1 mg/m³ after 6 weeks. Weakness of the hind legs and degeneration of the skeletal muscle fibres were observed only in the high concentration group in 4 females and a significant increase in urine volume and reduced body weights (–12%) were determined in the female rats. Treatment-induced effects were not observed in the lungs and the respiratory tract (3 planes of section in the nasal conchae, trachea) in any of the groups. The brain was examined only in the control group and in the high exposure group; no unusual findings were determined (Olin 1989 c). Therefore, the NOAEC (no observed adverse effect concentration) in this study was 1.1 mg/m³. As the animals were exposed whole-body, also oral absorption of the substance through grooming can be assumed.

5.2.2 Oral administration

The studies reviewed in the 1994 documentation with repeated oral exposure to sodium pyrithione in rats and monkeys (Greim 1998) that are relevant for the evaluation are shown in Table 2 together with studies in rats that have become available since then.

The most sensitive end point in rats after exposure to doses of 2 mg/kg body weight and day and above for 13 weeks was atrophy of the hind leg muscles, while degeneration and necrosis of the muscle fibres and restrictions in mobility were observed in a 52-week study at doses of 1.4 mg/kg body weight and day and above. After 2 years, degenerative changes in the sciatic nerve and neurogenic atrophy of the skeletal muscles were reported at doses of 0.5 mg/kg body weight and day and above. In a 4-week study in monkeys, vomiting was observed at doses of 15 mg/kg body weight and day and above and loss of appetite at doses of 200 mg/kg body weight and day and above. In a 52-week study, vomiting and effects on haematology and organ weights were observed at doses of 5 mg/kg body weight and day and above. Neurotoxicity did not occur up to a dose of 150 mg/kg body weight and day. For a period of several weeks during the chronic study, vomiting was induced in most of the animals of the low dose group and in all animals of the medium and high dose groups about 15 to 30 minutes after administration of the substance. This effect was not observed in the control animals. At the end of the study, the blood plasma concentrations (mean value ± standard deviation) of the main metabolite 2-methylsulfonyl pyridine were determined to be 1.13 ± 0.551, 4.60 ± 3.022 and 7.11 ± 3.036 µg/ml in the low, medium and high dose groups, respectively (Olin 1989 a). Vomiting was induced in 10 animals of the low dose group for an average of 4.7 of 52 weeks, which is equivalent to a reduction of the dose by about 10%. At the medium dose

of 25 mg/kg body weight and day, the concentration of 2-methylsulfonyl pyridine was proportional to the applied dose. No proportionality was evident at the high dose of 75 mg/kg body weight and day, probably because of the vomiting. It is therefore to be assumed that the majority of the administered substance was absorbed at the low and medium dose.

In a study previously reviewed in the 1994 documentation (Greim 1998), dogs were given daily gavage doses of sodium pyrithione of 0.1 to 40 mg/kg body weight and day for a period of 1 to 6 days. Vomiting, mydriasis, impaired vision and loss of the light reflex were observed (Moe et al. 1960 in Greim 1998).

Tab. 2 Studies of the toxicity of sodium pyrithione after repeated oral administration

Species, strain, number per group	Exposure	Findings	References
rat, CD, 20 ♂, 20 ♀	**13** weeks, 0, 0.5, 2, 8 mg/kg body weight and day, 7 days/week, gavage	**0.5 mg/kg body weight**: **NOAEL**; **2 mg/kg body weight**: bilateral atrophy of the hind leg muscles (♂: 5/20, ♀: 6/20) and of the subcutaneous panniculus muscle (♀: 3/20); **8 mg/kg body weight**: progressive paralysis of the hind legs (♂: 4/20, ♀: 16/20), body weight gains ↓, final body weights ↓ (2% lower than controls), reduced feed consumption (–10%), emaciation, grip strength of the hind legs ↓, landing foot splay ↓, bilateral atrophy of the hind leg muscles (♂: 19/20, ♀: 20/20), paravertebral muscles (♂: 2/20, ♀: 17/20) and the subcutaneous panniculus muscle (♂: 17/20, ♀: 20/20); ♀: mortality 10/20	Olin 1988 c
rat, CD, 10 ♂, 10 ♀	**90** days, 0, 0.1, 0.5, 2.5 mg/kg body weight and day, 7 days/week, gavage	**0.1 mg/kg body weight and above**: hepatocellular hypertrophy ↑ (maximum grade 2 of 5); **0.5 mg/kg body weight**: **NOAEL**; **2.5 mg/kg body weight**: salivation ↑, reddish-brown discoloration around the muzzle, water consumption ↑, ♀: liver: absolute and relative weights ↑ (+10% and +13%, respectively), mononuclear cell infiltrates ↑ (maximum grade 2 of 5); bent posture, accelerated breathing and walking on the toes in 1/10 from day 71; body weights, feed consumption and sperm parameters unchanged, no unusual findings in functional observation battery	Weyl 1997
rat, Sprague Dawley, 12 ♂, 12 ♀, high dose: 20 ♂, 20 ♀	**52** weeks, 0, 0.5, 1.4, 4/2.8 (♂)/4/2.8/2.1 (♀)[a] mg/kg body weight and day, 7 days/week, gavage	**0 mg/kg body weight**: ♀: mortality 1/12; **0.5 mg/kg body weight**: ♀: mortality 2/12; **1.4 mg/kg body weight**: landing foot splay ↓; ♂: mortality 1/12, ataxia 1/12; ♀: mortality 1/12, body weights ↓ (not significant), slight to marked mobility restrictions, sciatic nerve: slight nerve fibre degeneration 1/11, skeletal muscles: slight to marked degeneration and necrosis 9/11 and atrophy of the muscle fibres 7/11; **4/2.8/2.1 mg/kg body weight**: body weights ↓, landing foot splay ↓; ♂: mortality 1/20, ataxia 2/20, slight to marked mobility restrictions and pronation 1/20; skeletal muscles: degeneration, necrosis and atrophy of the muscle fibres 8/19, not statistically significant; ♀: mortality 3/20, emaciation, ataxia 4/20, slight to marked mobility restrictions, absolute and relative[g] heart weights ↓, sciatic nerve: enlarged 5/17, slight to moderate nerve fibre degeneration 5/17, skeletal muscles: size ↓ 10/17, slight to marked degeneration, necrosis and atrophy of the muscle fibres 16/17	Rütgers Chemicals 2004

Tab. 2 *(continued)*

Species, strain, number per group	Exposure	Findings	References
rat, CD, 20 ♂, 20 ♀	**2 years**, 0, 0.5, 1.5, 3.5[b] mg/kg body weight and day, 7 days/week, gavage	**0.5 mg/kg body weight**: ♂: serum: glucose ↑ (only week 53), chloride ↓ (only week 53); ♀: week 104: haemoglobin levels ↓ (–10%), haematocrit ↓ (–12%), erythrocyte count ↓ (–13%); serum: creatine phosphokinase activity ↑ (only week 78); **1.5 mg/kg body weight**: ♂: atrophy of the hind leg muscles, relative lung weights ↑ (+17%), serum: glucose ↑ (only week 53), chloride ↓ (only week 53); ♀: erythrocyte count ↓ (weeks 27 and 53, not weeks 78 and 104); serum: glucose ↑ (only week 104), sodium ↑ (only week 78), creatine phosphokinase activity ↑ (only week 78); **3.5 mg/kg body weight**: ♂ and ♀: weakness of the hind legs, atrophy of the hind leg muscles, degeneration of the sciatic nerve, eyes: retinal atrophy; ♂: relative liver weights ↑ (+15%), relative lung weights ↑ (+23%), serum: glucose ↑ (only week 53), chloride ↓ (only week 53); ♀: body weight gains ↓ (–19%), degeneration of the nerve fibres in the spinal medulla; erythrocyte count ↓ (weeks 27 and 53, not weeks 78 and 104); serum: glucose ↑ (only week 104), sodium ↑ (only week 78), aspartate aminotransferase and γ-glutamyl transferase activity ↓ (only week 53), creatine phosphokinase activity ↑ (only week 78); see also Section 5.7	Olin 1991 b
rat, Sprague Dawley, 52 ♂, 52 ♀	**2 years**, 0, 0.5, 1.4, 2.8 (♂)/2.1 (♀)[a] mg/kg body weight and day, 7 days/week, gavage	**0 mg/kg body weight**: ♂: mortality after 104 weeks: 71.4%; ♀: mortality after 104 weeks: 46.4%; **0.5 mg/kg body weight**: ♂: discontinued in week 98 because of high mortality (75%); body weights ↓ (from week 73); ♀: mortality after 104 weeks: 48.2%; body weights ↓ (only weeks 101 and 104); **0.5 mg/kg body weight and above**: muscle tone ↓; sciatic nerve: degenerative changes, loss of nerve fibres and replacement with connective tissue; skeletal muscles: degenerative changes, neurogenic atrophy; ♀: ataxia, emaciation, skeletal muscles: replacement of muscle fibres with adipose and connective tissue; **1.4 mg/kg body weight**: ♂: mortality after 104 weeks: 73.2%; body weights ↓ (from week 73); ♀: mortality after 104 weeks: 60.7%; body weights ↓ (from week 25); **1.4 mg/kg body weight and above**: ♂: ataxia, skeletal muscles: replacement of muscle fibres with adipose tissue; ♀: weakness of the hind legs, pronation, bent posture, body weights ↓ (from week 25), absolute and relative[g] kidney and spleen weights ↓; **2.8/2.1 mg/kg body weight**: body weights ↓; ♂: mortality after 104 weeks: 73.2%; forestomach: acanthosis, hyperkeratosis; ♀: mortality after 104 weeks: 67.9%; swollen abdomen, feed consumption ↓; see also Section 5.7	Rütgers Chemicals 2004
monkey, Macaca fascicularis, 1 ♂, 1 ♀	**4 weeks**, 0, 1/100/400[c], 5/1200[d], 15, 50/200/800[e] mg/kg body weight and day, 7 days/week, gavage	**1/100/400 mg/kg body weight**: vomiting at 400 mg/kg body weight; **5/1200 mg/kg body weight**: vomiting at 1200 mg/kg body weight; ♀: mortality (last day of study); **15 mg/kg body weight**: occasional vomiting during the last week; **50/200/800 mg/kg body weight**: loss of appetite at 200 mg/kg body weight, vomiting at 800 mg/kg body weight; no histopathological examination	Olin 1988 a

Tab. 2 *(continued)*

Species, strain, number per group	Exposure	Findings	References
monkey, Macaca fascicularis, 5 ♂, 5 ♀	**52** weeks, 0, 5, 25, 150/75[f] mg/kg body weight and day, 7 days/week, gavage	**5 mg/kg body weight and above**: occasional vomiting, erythrocyte count ↓; ♂: relative kidney weights ↑ (+30%, +26%, +24%); **25 mg/kg body weight and above**: haemoglobin and haematocrit levels ↓; ♂: relative liver weights ↑ (+17%, +30%); **150/75 mg/kg body weight**: mortality: 1/5 ♂, 2/5 ♀; salivation ↑ (week 1); ♀: relative liver weights ↑ (+36%), absolute adrenal gland weights ↑ (+38%); no findings in sciatic nerve, skeletal muscles and brain	Olin 1989 a

[a] dose reduced from 4 to 2.8 mg/kg body weight and day (♂ and ♀) after 6 weeks and to 2.1 mg/kg body weight and day (only ♀) after 9 months
[b] dose reduced from 5 to 3.5 mg/kg body weight and day after 12 weeks
[c] dose increased from 1 to 100 mg/kg body weight and day after 16 days and to 400 mg/kg body weight and day after 23 days
[d] dose increased from 5 to 1200 mg/kg body weight and day after 23 days
[e] dose increased from 50 to 200 mg/kg body weight and day after 16 days and to 800 mg/kg body weight and day after 23 days
[f] dose reduced from 150 to 75 mg/kg body weight and day after 6 weeks
[g] relative to the brain weights
NOAEL: no observed adverse effect level

5.2.3 Dermal application

There are no new studies available.

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

After a single application to the rabbit skin, sodium pyrithione (40% aqueous solution, 4 hours, occlusive) induced mild oedema and erythema, which subsided after 72 hours (Olin 1987 d in Greim 1998).

A 50% suspension of sodium pyrithione in Aquaphor® ointment applied daily to the shaved dorsal skin of Yorkshire pigs (25 applications, 8 application sites per animal, changed daily, each 20 × 19 cm^2, duration of application 8 hours) at doses of 10, 30 or 100 mg/kg body weight and day was corrosive (Olin 1974 b in Greim 1998).

In a study carried out according to OECD Test Guideline 404, 0.5 g of sodium pyrithione (purity 92.5%), moistened with water, were applied to the shaved dorsal skin of 3 female New Zealand White rabbits. The test substance was applied semi-occlusively for 4 hours and the remaining substance was then removed. Systemic toxic effects did not occur. Severe erythema with scabbing was observed in 2 of 3 animals (mean scores after 24, 48 and 72 hours: 0.0/3.3/2.3 on a scale with a maximum of 4). Oedema was found in all animals at the end of the application period; this was reversible in 1 animal after only 24 hours, in the other 2 animals after 6 and 10 days, respectively. Therefore, all skin lesions were reversible within 14 days, and the test substance was considered a skin irritant (Rütgers Organics 2001 a).

5.3.2 Eyes

Sodium pyrithione in a 40% aqueous solution (0.1 ml) temporarily induced slight clouding of the cornea in 2 of 6 rabbits 24 hours after administration. Slight redness of the conjunctiva was observed in all animals, which had not subsided in 2 of 6 animals after 72 hours. Redness of the conjunctiva was observed also after application of the substance in powder form (10 mg) (Olin 1967 a, b in Greim 1998).

Sodium pyrithione powder was placed in the conjunctival sac of 1 eye of 3 male and 3 female New Zealand White rabbits in an amount of 0.1 cm^3 (about 84 mg). Four of 6 animals died within 1 day. They had exhibited lethargy, limp muscle tone, exhaustion, convulsions, tachypnoea, eye discharge and wetness in addition to reddening around the nose. Unusual findings (no other details) were determined in the lungs, liver and gastrointestinal tract at necropsy. Irritation of the conjunctiva was found in the 2 surviving animals, which was reversible up to day 7. Iritis was observed in 1 animal only on the first day; there was no corneal opacity. Clinical signs in the surviving animals were lethargy and wetness and yellow discoloration around the nose. Total scores of 12 to 21 of 110 were determined for all

animals after 1 hour, while scores of 12, 6 to 12 and 0 to 4 were reported for the surviving animals after 1, 2 or 3 days, respectively (Olin 1995).

Instillation of a 40% aqueous solution of sodium pyrithione (0.1 ml) into the conjunctival sac of 1 eye caused iritis in all 6 female New Zealand White rabbits, which was reversible within 2 days. In addition, irritation of the conjunctiva was observed in all animals and was reversible after 14 days. Corneal opacity was not observed. A total score of 17 of 110 was determined for all animals after 1 hour, while scores of 10 to 12, 4 to 6 and 2 to 6 were reported for the surviving animals after 1, 2 or 3 days, respectively. Three animals had died by day 2; they had exhibited lethargy, exhaustion, diarrhoea, soiling in the anogenital area, convulsions, tachypnoea, ataxia and wetness around the nose. Unusual findings (no other details) were obtained in the lungs, peritoneum and gastrointestinal tract at necropsy. Lethargy, yellow nasal discharge and yellow discoloration around the nose were observed in the surviving animals (Olin 1996).

Instillation of a 40% aqueous solution of sodium pyrithione (0.01 ml) into the conjunctival sac of 1 eye of 6 female New Zealand White rabbits induced irritation of the conjunctiva in all animals, which was reversible by day 3 in the animals that survived. Corneal opacity was observed in 1 animal only on day 1. Iritis was detected in 2 animals also only on day 1. Total scores of 4 to 10 of 110 were determined for all animals after 1 hour, while scores of 0 to 5, 0 and 0 were reported for the surviving animals after 1, 2 or 3 days, respectively. Two animals had died by day 2; they had exhibited convulsions, exhaustion, shallow breathing, wetness around the nose and abnormal posture. Yellow nasal discharge and wetness around the nose were observed in 1 animal that survived (Olin 1998).

Irritation was not induced after 1 drop of a 0.0625%, 0.625% or 6.25% sodium pyrithione solution in a 1% soap solution was instilled into the conjunctival sac of monkeys, followed by rinsing (no other details) (Olin 1969 a in Greim 1998).

A 40% aqueous sodium pyrithione solution was instilled into the conjunctival sac of 1 eye of 1 female and 2 male monkeys (Macaca fascicularis) in an amount of 0.1 ml per eye. Conjunctival redness was observed in both male animals (animal 1: maximum score 1 of 3 beginning after 1 hour; animal 2: maximum score 2 of 3 after 48 hours), which was reversible after 7 days. There were no findings in the cornea and iris and in the female also any findings in the conjunctiva. Signs of systemic toxicity were not observed (Olin 1997).

5.4 Allergenic effects

5.4.1 Sensitizing effects on the skin

A weakly positive reaction was obtained in a maximization test, which did not lead to a legal classification (Olin 1987 e in Greim 1998), and contact sensitizing effects were not observed in an earlier test with intradermal application (Olin 1969 b in Greim 1998, see below). Sodium pyrithione did not yield positive results in another maximization test with 20 Dunkin Hartley guinea pigs (92.5%, loss on drying 7.5%; no minor constituents in amounts of more than 0.2%). After pre-treatment of the test area with 10% sodium lauryl sulfate in petrolatum, the animals were treated for induction by intradermal application of a 5% formulation in physiological saline and occlusive topical application of a 50% formulation in water. Four of the animals died 3 to 6 days after the topical induction, possibly because of substance-related effects. However, details are not given. At the challenge treatment, 1 of 10 control animals exhibited very slight erythema after 24 and 48 hours. By contrast, 1 of the remaining 16 pre-treated animals reacted with marked erythema after 24 hours and 1 with severe erythema or oedema after 48 hours (Rütgers Organics 2002 f).

5.4.2 Photocontact sensitization

In a modified Draize test, intradermal induction with a 2% formulation did not cause contact sensitization, but slight erythema in 3 of 10 albino guinea pigs after the challenge with a 0.1% formulation and UV radiation (290–320 nm) (Olin 1969 b in Greim 1998). However, this result is not relevant for the assessment of the photocontact sensitizing effects of sodium pyrithione because of the short-wave UV light used. In a test with open application of 40% sodium pyrithione followed by treatment with UV-A/UV-B radiation, only 1 animal in each group of 12 albino guinea pigs responded at the challenge treatment with 4%, 8% and 40% formulations (Olin 1981 in Greim 1998).

The photocontact allergenic potential of sodium pyrithione was investigated using a modified mouse ear swelling test in BALB/c mice pre-treated with cyclophosphamide. The animals were given a single intraperitoneal injection of cyclophosphamide at a dose of 200 mg/kg body weight 3 days before the induction treatment. The animals were treated

for induction with 50 µl of a 5% formulation of sodium pyrithione in acetone/corn oil (4:1) applied to the dorsal skin on 3 consecutive days, followed by irradiation with UV-A (10 J/cm^2) and then UV-B (45 mJ/cm^2). The challenge treatment was carried out 7 days later by applying 8 µl of a 1% formulation to each side of the ears. UV-A/UV-B irradiation was carried out 1 hour after application. The average ear swelling response obtained with sodium pyrithione (4.6×10^{-2} mm) was of a similar magnitude to that of several known photoallergens that were examined concurrently, such as bisphenol A (2.1×10^{-2} mm), bithionol (4.2×10^{-2} mm), chlorpromazine (7.4×10^{-2} mm) or musk ambrette (5.8×10^{-2} mm). Like for the other substances mentioned above, the tests did not yield evidence of contact allergenic effects. In the animals that underwent only one challenge treatment (control for a phototoxic effect), markedly weaker reactions were observed in response to sodium pyrithione (1.8×10^{-2} mm) and the other substances ($0.5–1.5 \times 10^{-2}$ mm) (Gerberick and Ryan 1990).

Preliminary positive findings were reported by other authors following testing using another modified mouse ear model (Maguire and Kaidbey 1982); however, these findings were not documented and are therefore not relevant for the evaluation.

An in vitro study that investigated the photochemical binding of sodium pyrithione to human plasma protein (equimolar ratio of sodium pyrithione to protein; 3.5×10^{-5} M in 0.1 M Tris-HCl buffer; pH 8.1; irradiation at room temperature, 313 nm) concluded that binding to albumin was likely because the long-wave absorption maximum of sodium pyrithione (330 nm) disappeared after UV irradiation (Barratt and Brown 1985).

5.4.3 Sensitizing effects on the airways

There are no studies available.

5.5 Reproductive and developmental toxicity

The 1994 documentation (Greim 1998) and the 2012 supplement (Hartwig 2012 a) reviewed the data for developmental toxicity available at that time. The following discusses the studies that have been published since then and provides an overview of all the studies relevant to the evaluation.

5.5.1 Fertility

In a 2-generation study, sodium pyrithione impaired fertility and mating behaviour in male F0 animals (Sprague Dawley rats) at the highest dose tested of 3.5 mg/kg body weight and day (gavage, maternally toxic during and after gestation). The gestation period, litter size and reproductive organs were not affected in F0 and F1 animals. Dose-dependent muscle atrophy of the upper hind legs was found in the parent animals. No significant external malformations were observed in the F1 and F2 generations (see also Table 3) (Olin 1989 b; see also Greim 1998).

In another 2-generation study, Sprague Dawley rats were given gavage doses of sodium pyrithione of 0, 0.7, 1.4 or 2.8 mg/kg body weight and day. Body weights, body weight gains and feed consumption were reduced in the male F0 animals of the high dose group. No unusual findings were obtained in the microscopic examination of the adrenal glands, epididymis, pituitary gland, prostate gland, seminal vesicles with coagulation glands and testes. A slight decrease in the fertility index in the medium and high dose groups was not assessed as toxicologically relevant by the authors, as the sperm parameters (motility, morphology, concentration, daily sperm production and spermatogenesis cycle) were not affected by the treatment. Body weights, body weight gains and feed consumption were reduced in the female F0 animals of the medium and high dose groups and the body weights of the offspring were significantly reduced on lactation day 21 and lactation days 14 and 21, respectively. No unusual findings were obtained in the microscopic examination of the adrenal glands, ovaries, pituitary gland, uterus with fallopian tubes, cervix and vagina.

Body weights and body weight gains were reduced also in F1 animals of the high dose group and the feed consumption was intermittently reduced in the females. No unusual findings were obtained in the microscopic examination of the above-mentioned organs in male and female F1 animals. The body weights of the offspring (F2) were reduced on lactation days 14 and 21 and on lactation day 14 in the medium and high dose groups, respectively. The authors reported a NOAEL (no observed adverse effect level) for toxicity in the females of 0.7 mg/kg body weight and day and in the males of 1.4 mg/kg body weight and day (Rütgers Organics 2003). The NOAEL for fertility was 2.8 mg/kg body weight and day, the highest dose tested.

5.5.2 Developmental toxicity

The studies of the developmental toxicity induced by sodium pyrithione that are relevant for the evaluation are shown in Table 3.

In a prenatal developmental toxicity study carried out according to OECD Test Guideline 414, Sprague Dawley rats were given sodium pyrithione (40.8% aqueous solution) in gavage doses of 0, 1, 2 or 4 mg/kg body weight and day from gestation days 6 to 19. Maternal toxicity was evident in the high dose group in the form of difficulties in movement and impairment of the hind legs, bent posture and reduced body weights, feed consumption and uterus weights. Developmental delays in the form of reduced foetal weights and slightly delayed ossification (sternal segments, metacarpal and metatarsal bones) were determined in the foetuses of the high dose group. In addition, the percentage of small foetuses was increased in this group. The NOAEL for maternal and developmental toxicity was 2 mg/kg body weight and day (Rütgers Organics 2002 d).

In a prenatal developmental toxicity study in CD rats with dermal application from gestation days 6 to 15, reduced foetal weights and skeletal changes (bent ribs and extremities) were observed in the foetuses at a dose of 7 mg/kg body weight and day with severe concurrent maternal toxicity that was manifest as increased mortality and reduced body weight gains. The NOAEL for maternal and developmental toxicity was 3 mg/kg body weight and day (Olin 1980 in Greim 1998).

In a prenatal developmental toxicity study in rabbits with dermal application from gestation days 6 to 19, no effects on the foetuses were reported up to the highest dose tested of 5 mg/kg body weight and day (Olin 1987 j in Greim 1998).

In a 2-generation study, Sprague Dawley rats were given sodium pyrithione in gavage doses of 0, 0.5, 1.5 or 3.5 mg/kg body weight and day. In the parent animals, muscle atrophy was observed at doses of 1.5 mg/kg body weight and day and above and delayed body weight gains at 3.5 mg/kg body weight and day. Slight delays in development were found in the offspring at 3.5 mg/kg body weight and day. Teratogenic effects were not reported. At a dose of 3.5 mg/kg body weight and day, a reduction in the startle response was observed in the postnatal behavioural development of F1 offspring (Olin 1989 b, see also Greim 1998).

In another 2-generation study in Sprague Dawley rats, the animals were given gavage doses of sodium pyrithione of 0, 0.7, 1.4 or 2.8 mg/kg body weight and day. Decreased body weights and an increased number of offspring with cryptorchidism were observed in F1 offspring exposed at the medium dose and above, and preputial separation was slightly delayed in the high dose group. The mean body weights and the litter weights were reduced in F2 offspring at doses of 1.4 mg/kg body weight and day and above and the number of offspring with cryptorchidism was increased at the high dose. Survival was reduced on postnatal day 4 only in the medium dose group. The NOAEL for perinatal and postnatal toxicity was 0.7 mg/kg body weight and day (Rütgers Organics 2003).

The 2 studies described in the 1994 documentation and in the 2012 supplement with oral administration of sodium pyrithione to rats (Olin 1972 in Greim 1998; Olin 1976 in Hartwig 2012 a) and the study described in the 1994 documentation with dermal application to pigs (Olin 1974 b in Greim 1998) were carried out from 1972 to 1974 at the contract laboratory Industrial Bio-Test Laboratories (IBT). Irregularities were found in the testing and documentation procedures used by IBT for studies performed at this time (OECD 2005). Therefore, the studies are of questionable quality.

The results of recent developmental toxicity studies performed with gavage administration (Rütgers Organics 2002 d) confirm the findings reported by the dermal exposure study at the dose of 7 mg/kg body weight and day (Olin 1980 in Greim 1998) and the oral exposure studies at 7.5 mg/kg body weight and day (Olin 1972 in Greim 1998; Olin 1976 in Hartwig 2012 a) and yield a clear NOAEL for developmental toxicity of 2 mg/kg body weight and day after oral exposure.

Tab. 3 Studies of the developmental toxicity of sodium pyrithione in rats and rabbits

Species, strain, number per group	Exposure	Findings	References
Prenatal developmental toxicity			
rat, Sprague Dawley, 24 ♀	**gestation days 6–19**, 0, 1, 2, 4 mg/kg body weight and day, **gavage**, in water, examination: gestation day 20, purity: 40.8% (aqueous solution)	**2 mg/kg body weight**: dams: **NOAEL maternal toxicity**; foetuses: **NOAEL developmental toxicity**; **4 mg/kg body weight**: dams: body weight gains and feed consumption ↓; difficulties with movement (21/24), impairment of the hind legs (7/24), bent posture (3/24), emaciation (2/24); uterus weights ↓ (–19%); foetuses: mean body weights ↓; percentage of small foetuses ↑ (11.3%, controls: 0.3%), incomplete ossification of sternal segments (6th), metacarpal and metatarsal bones; no teratogenicity	Rütgers Organics 2002 d
rat, CD, 25 ♀	**gestation days 6–15**, 0, 0.5, 1.5, 3.0, 7.0 mg/kg body weight and day, **dermal**, in Aquaphor ointment, examination: gestation day 20, purity: 93.6%	**0.5 mg/kg body weight**: dams: erythema (16%); **1.5 mg/kg body weight**: dams: erythema (64%); **3.0 mg/kg body weight**: dams: erythema (96%), **NOAEL maternal toxicity**; foetuses: **NOAEL developmental toxicity**; **7.0 mg/kg body weight**: dams: erythema (100%), kyphosis, soiled fur around the anogenital area, immobility of the extremities, body weight gains ↓ (25%), mortality 5/25 (gestation days 17–20), thymus gland size ↓ (7/25); foetuses: foetal weights ↓, late resorptions and post-implantation losses ↑, malformations (57/167, controls: 7/199): bent ribs (54/167, controls: 7/199) and extremities (19/167, controls 0), reduced ossification of the skull, sternal segments, metacarpal and metatarsal bones	Olin 1980 in Greim 1998
rabbit, New Zealand White, 20 ♀	**gestation days 6–19**, 0, 1.0, 2.5, 5.0 mg/kg body weight and day, **dermal**, in water, examination: gestation day 29, purity: 43.83% (aqueous solution)	**2.5 mg/kg body weight**: dams: NOAEL maternal toxicity; **5.0 mg/kg body weight**: dams: body weight gains ↓ (gestation days 6–20); foetuses: **NOAEL developmental toxicity**	Olin 1987 j in Greim 1998
Prenatal and postnatal developmental toxicity			
rat, Sprague Dawley, 25 ♂, 25 ♀	**2-generation study**, 0, 0.5, 1.5, 3.5[a)] mg/kg body weight and day, F0: ♂ and ♀ 77 days before and during mating, ♀ additionally up to 25 days post-partum, F1: ♂ and ♀ 98 days before mating, ♀ additionally up to 21 days post-partum, gavage, in water, examination: postnatal days 1–21, purity: 41.2% (aqueous solution)	**0.5 mg/kg body weight**: **NOAEL parental toxicity**; **1.5 mg/kg body weight**: **NOAEL postnatal toxicity**; parent animals: ♀: muscle atrophy of the upper hind limbs, number of sarcolemmal nuclei and fat deposits in the muscle fibres in 3/25 F1 animals ↑; **3.5 mg/kg body weight**: parent animals: ♀: 1 F0, 2 F1 sacrificed in extremis; retardation of body weight gains during and after gestation, feed consumption ↓ (F1), fertility index in F0 animals ↓, muscle atrophy of the upper hind limbs, number of sarcolemmal nuclei and fat deposits in the muscle fibres in 19/25 F0 animals and 20/25 F1 animals ↑; ♂: retardation of body weight gains, copulation and fertility indices in F0 animals ↓, muscle atrophy of the upper hind limbs, number of sarcolemmal nuclei and fat deposits in the muscle fibres in 8/25 F0 animals and 9/25 F1 animals ↑; offspring: **NOAEL perinatal toxicity up to postnatal day 4**, startle response (F1: postnatal day 15) ↓; ♀: body weights ↓ (F1: postnatal days 14 and 21; F2: postnatal day 21 (not significant)); external malformations in none of the dose groups	Olin 1989 b (see also Greim 1998)

Tab. 3 *(continued)*

Species, strain, number per group	Exposure	Findings	References
rat, Sprague Dawley, 24–32 ♂, 24–32 ♀	**2-generation study**, 0, 0.7, 1.4, 2.8 mg/kg body weight and day, ♂ and ♀ 70 days before and during mating, ♀ additionally up to 21 days post-partum, gavage, in water, examination: postnatal days 1–21, purity: 40.8% (aqueous solution)	**0.7 mg/kg body weight**: parent animals: **NOAEL maternal toxicity**; offspring: **NOAEL perinatal and postnatal toxicity**; **1.4 mg/kg body weight**: parent animals: ♀: body weights, body weight gains and feed consumption ↓; ♂: **NOAEL**; F1 offspring: body weights ↓ (postnatal day 21); number of small offspring ↑; ♂: number of offspring with cryptorchidism ↑ (a few cases); F2 offspring: survival on postnatal day 4 ↓ (no dose–response relationship), mean body weight and litter size ↓ (postnatal days 14 and 21); **2.8 mg/kg body weight**: parent animals: ♂ and ♀: body weights, body weight gains and feed consumption ↓; F1 offspring: body weights ↓ (postnatal days 14 and 21); number of small offspring ↑; ♂: number of offspring with cryptorchidism ↑ (a few cases), slightly delayed preputial separation; F2 offspring: mean body weights and litter size ↓ (from postnatal days 7 to 21); ♂: number of offspring with cryptorchidism ↑	Rütgers Organics 2003

[a] weeks 1 to 3: 4.5 mg/kg body weight and day

Summary: In a developmental toxicity study in rats, foetotoxicity and incomplete ossification of sternal segments, metacarpal and metatarsal bones were found in the foetuses given gavage doses of 4 mg/kg body weight and day and above. The NOAEL for developmental toxicity in rats was 2 mg/kg body weight and day after oral exposure (Rütgers Organics 2002 d). After dermal application of 7 mg/kg body weight and day, reduced body weights and decreased ossification of ribs and extremities were observed in the foetuses of the same species (Olin 1980 in Greim 1998). After dermal application, the NOAEL for developmental toxicity in rats was 3 mg/kg body weight and day. No effects of developmental toxicity were found in New Zealand White rabbits after dermal application of doses up to 5 mg/kg body weight and day (Olin 1987 j in Greim 1998). In all 3 studies, maternal toxicity was already observed at the NOAEL for developmental toxicity.

In the two 2-generation studies in Sprague Dawley rats, perinatal effects on the offspring were not observed up to postnatal day 4 after gavage administration of 3.5 (Olin 1989 b; see also Greim 1998) or 0.7 mg/kg body weight and day (Rütgers Organics 2003). In the second 2-generation study, reduced mean body weights and reduced litter weights were reported for F2 offspring on postnatal days 14 and 21 at doses of 1.4 mg/kg body weight and day and above. Reduced body weights were observed in F1 offspring on postnatal day 21 only at doses of 2.8 mg/kg body weight and day and above (Rütgers Organics 2003).

5.6 Genotoxicity

5.6.1 In vitro

The cytotoxicity of sodium pyrithione limits the validity of in vitro genotoxicity studies as testing can be performed only with low concentrations.

Negative findings were reported by the studies of sodium pyrithione described in the 1994 documentation (Greim 1998), a Salmonella mutagenicity test, a UDS (DNA repair synthesis) test in rat hepatocytes and an HPRT gene mutation test.

Sodium pyrithione was investigated (40% solution, all data refer to the active ingredient) in Salmonella mutagenicity tests with the strains TA98, TA100, TA102, TA1535 and TA1537 both in the presence and absence of metabolic activation (S9 mix). As a result of the severe cytotoxicity, the maximum concentration tested was 100 µg/plate. The number of revertants was not doubled in 2 independent tests, a plate incorporation test with concentrations from 6.25 to

100 µg/plate and a preincubation test with concentrations from 3.13 to 100 µg/plate (TA1537: 1.56 to 50 µg/plate). The positive controls yielded the expected results (Rütgers Organics 2002 e).

In a chromosomal aberration test in V79 cells, sodium pyrithione (40% solution, all data refer to the active ingredient) was tested in concentrations of 0.313 to 80.0 µg/ml for a treatment period of 3 hours with and without metabolic activation (S9 mix). After 20 hours, the number of cells was determined. In the absence of metabolic activation, the number of living cells was reduced to 62% to 75% of the number in the controls. No toxicity was observed at the highest concentration in the presence of S9 mix; the number of cells was reduced to 89% of the number in the controls. The number of cells was 66% of that of the controls at 40.0 and 20.0 µg/ml and 76% to 104% at the remaining concentrations. Therefore, concentrations of 20, 40 and 80 µg/ml were selected for the evaluation of chromosomal aberrations. In the absence of metabolic activation, a statistically significant increase in aberrations without gaps was observed with concurrent cytotoxicity at all concentrations. In the presence of metabolic activation, the increase in the frequency of aberrations without gaps was statistically significant at concentrations of 40.0 µg/ml and above; however, cytotoxicity also occurred in these cases. The positive controls yielded the expected results (Rütgers Organics 2002 a).

Sodium pyrithione (40% solution, all data refer to the active ingredient) was examined in an HPRT test in V79 cells. Cytotoxicity was measured as the impact on the ability to form colonies without metabolic activation; at concentrations of 313 µg/ml and above this ability was reduced to 42% of the level of the controls and at the concentration of 1250 µg/ml to 10% of the level of the controls. In the presence of S9 mix, the ability to form colonies was 50% of the level of the controls at the concentration of 156 µg/ml and 11% at the concentration of 313 µg/ml. At concentrations of 2500 µg/ml and above it was 0% in both the absence and presence of metabolic activation. Two tests each were performed with concentrations in a range from 78.1 to 1875 µg/ml without metabolic activation and with concentrations from 19.5 to 470 µg/ml in the presence of S9 mix. The HPRT test yielded negative results, the positive controls yielded the expected results (Rütgers Organics 2002 b).

5.6.2 In vivo

Negative results were obtained in a micronucleus test with male and female CD-1 mice given intraperitoneal injections of sodium pyrithione at a dose of 238 mg/kg body weight and day (Olin 1987 g in Greim 1998).

Another micronucleus test was carried out with male and female NMRI mice. Groups of 5 animals per sex, dose and point in time were given sodium pyrithione in a single gavage dose of 0, 400, 482 or 580 mg/kg body weight. The animals were sacrificed after 24 hours and the bone marrow was examined. An additional control group and an additional high dose group were examined after 48 hours. A statistically significant increase in the incidence of micronuclei was not found in either polychromatic or normochromatic erythrocytes. One male of the high dose group died 2 hours after the injection and was replaced by an animal that was treated according to an identical procedure. Convulsions were induced in 1 male and 1 female of the high dose group. In the males of this group, the number of polychromatic erythrocytes and the ratio of polychromatic to normochromatic erythrocytes were significantly reduced after 48 hours. The bioavailability of the substance was demonstrated by the mortality induced and by the fact that the bone marrow was affected by the cytotoxicity at the high dose. The positive control, cyclophosphamide, yielded the expected results (Rütgers Organics 2002 c).

Conclusion: Sodium pyrithione yielded negative results in earlier in vitro genotoxicity studies, a Salmonella mutagenicity test, a UDS test in rat hepatocytes and an HPRT gene mutation test. Negative findings were obtained also by the studies that were performed since the publication of the 1994 documentation, a Salmonella mutagenicity test, and an HPRT test in V79 cells. Sodium pyrithione induced chromosomal aberrations in an in vitro test in V79 cells that was carried out since publication. However, negative results were obtained in 2 in vivo micronucleus tests in mice. For this reason, sodium pyrithione continues to be categorized as non-genotoxic.

5.7 Carcinogenicity

No signs of carcinogenic effects induced by sodium pyrithione were found in an oral carcinogenicity study in rats with doses of up to 3.5 mg/kg body weight and day (Olin 1991 b; see also Greim 1998).

Also a study with dermal application of sodium pyrithione to mice over a period of 80 weeks at doses of up to 40 mg/kg body weight and day did not yield evidence of a carcinogenic potential (Olin 1991 a; see also Greim 1998).

In a combined chronic toxicity and carcinogenicity study carried out according to OECD Test Guideline 453 (see also Section 5.2.2), groups of 52 male and 52 female Sprague Dawley rats were given daily sodium pyrithione gavage doses of 0, 0.5, 1.4 or 2.8/2.1 mg/kg body weight. The treatment period was 104 weeks, except for the males of the low dose group, which were sacrificed in week 98 of treatment because of the high mortality (75%). As a result of the severe toxicity, the high dose was reduced for the males from an initial 4.0 mg/kg body weight and day to 2.8 mg/kg body weight and day and for the females to 2.1 mg/kg body weight and day. In the males, the differences in mortality between the groups were not statistically significant; however, a slight increase in mortality was observed in the 0.5 mg/kg group. In the females, mortality was higher in the medium and high dose groups than in the control group. No treatment-related increase in the incidence of neoplasms was determined in the animals treated with sodium pyrithione (Rütgers Chemicals 2004).

6 Manifesto (MAK value/classification)

Neurotoxic effects are the critical effect in rats and rabbits, but not in monkeys.

MAK value. As there is no mechanistic explanation for the species differences in neurotoxicity, the derivation of the MAK value is based on studies in rats, the most sensitive species.

A NOAEC of 1.1 mg/m^3 was derived from an inhalation study in rats (Olin 1989 c); at this level, neither neurotoxicity nor treatment-related effects in the lungs and the respiratory tract occurred. After extrapolation from animal studies to humans (1:2) and taking into account the higher respiratory volume of humans at the workplace in comparison to the animal at rest under experimental conditions (1:2) and following application of the Preferred Value Approach, a MAK value of 0.2 mg/m^3 is derived for the inhalable fraction. On the basis of the data currently available, an intensification of the effects is not to be expected after chronic exposure.

A MAK value cannot be derived for zinc pyrithione because the substance is corrosive to the eyes and the inhalation study was carried out with a highly diluted aqueous suspension. Therefore, the irritation induced by undiluted zinc pyrithione has not been examined to a sufficient degree. By contrast, sodium pyrithione causes only slight irritation to the eyes, and thus leads to much weaker irritant effects than the zinc compound. Therefore, in spite of the fact that the inhalation study with sodium pyrithione was performed with a highly diluted aqueous solution, it is regarded as reliable, particularly because no irritation was induced in the respiratory tract up to the highest concentration tested of 8.1 mg/m^3. By contrast, clinical irritation was observed at zinc pyrithione concentrations of 2.5 mg/m^3 and above.

A MAK value of 0.2 mg/m^3 is also derived on the basis of the 2-year study in rats (Rütgers Chemicals 2004). From the LOAEL (lowest observed adverse effect level) of 0.5 mg/kg body weight an NAEL (no adverse effect level) (1:3) of 0.16 mg/kg body weight can be extrapolated. The following toxicokinetic data are taken into consideration for the extrapolation of this dose to a concentration in workplace air: the daily exposure of the animals in comparison with 5 days per week exposure at the workplace (7:5), the corresponding species-specific correction value for the rat (1:4), the assumed oral absorption (100%), the body weight (70 kg) and respiratory volume (10 m^3) of the person and the assumed 100% absorption by inhalation. The concentration calculated from this is 0.39 mg/m^3. As this value was calculated from data of an animal experiment, it is possible to derive a MAK value of 0.2 mg/m^3 for the inhalable fraction according to the procedures of the Commission (see List of MAK and BAT Values, Section I).

Peak limitation. As the MAK value is based on systemic effects, sodium pyrithione remains classified in Peak Limitation Category II. The initial half-life is between 0.7 and 2.8 hours. For this reason, the excursion factor of 2 has been retained.

Prenatal toxicity. The critical effects of prenatal toxicity are skeletal changes; these occur irrespective of the route of administration and cannot be attributed to reduced maternal body weight gains. In addition, an increased incidence of skeletal abnormalities of the ribs was observed after exposure to zinc pyrithione (Hartwig 2012 b).

In a developmental toxicity study, reduced mean body weights, an increased percentage of small foetuses and incomplete ossification of the sixth sternal segment and the metacarpal and metatarsal bones were observed in foetuses of rats given oral doses of 4 mg/kg body weight and day and above. The NOAEL was 2 mg/kg body weight and day.

In a developmental toxicity study in the same species, decreased body weights and reduced ossification of the ribs and extremities were observed in the foetuses after dermal application of 7 mg/kg body weight and day; the NOAEL was 3 mg/kg body weight (Olin 1980 in Greim 1998). No effects of developmental toxicity were found in New Zealand White rabbits given doses of up to 5 mg/kg body weight and day, the highest dose, by dermal application. All 3 studies reported concurrent maternal toxicity.

The following toxicokinetic data are taken into consideration for the extrapolation of the NOAELs of 2 and 3 mg/kg body weight in rats and 5 mg/kg body weight in rabbits to a concentration in workplace air: the corresponding species-specific correction values for the rat and the rabbit (1:4 and 1:2.4, respectively), the assumed absorption (oral or dermal 100%), the body weight (70 kg) and respiratory volume (10 m^3) of the person and the assumed 100% absorption by inhalation. The concentrations calculated from these values for the workplace are 3.5 (oral), 5.25 and 14.6 mg/m^3 (dermal), respectively. The 18-fold, 26-fold and 73-fold margins, respectively, between these values and the MAK value of 0.2 mg/m^3 are sufficiently large.

In the 2 available 2-generation studies, no effects on the offspring were observed in rats given gavage doses of 3.5 and 0.7 mg/kg body weight and day, respectively, up to postnatal day 4.

The values determined by toxicokinetic extrapolation (parameters as above, additional extrapolation from 7 days per week treatment to 5 days per week exposure at the workplace) were 8.6 and 3.4 mg/m^3, respectively. The 43-fold and 17-fold margins between these values and the MAK value of 0.2 mg/m^3 are sufficiently large. Even if the NOAEL for postnatal behavioural development of 1.5 mg/kg body weight and day is taken into consideration, the 19-fold margin to the MAK value of 0.2 mg/m^3 is sufficiently large. Therefore, as the MAK value has been markedly reduced, sodium pyrithione has been reclassified from Pregnancy Risk Group B in Pregnancy Risk Group C.

Germ cell mutagenicity. None of the available studies specifically investigated germ cell mutagenicity. Negative findings were obtained with sodium pyrithione in earlier in vitro genotoxicity studies, a Salmonella mutagenicity test, a UDS test in rat hepatocytes and an HPRT gene mutation test. Negative results were reported also by studies carried out since the 1994 documentation, a Salmonella mutagenicity test and an HPRT test in V79 cells. In a recent in vitro chromosomal aberration test in V79 cells, sodium pyrithione yielded positive results. By contrast, negative results were obtained in the 2 available in vivo micronucleus tests in mice. For this reason, sodium pyrithione continues to be regarded as non-genotoxic and has not been classified in a category for germ cell mutagens.

Carcinogenicity. Sodium pyrithione was not mutagenic in vitro and the clastogenic effects observed in vitro in V79 cells were not found in vivo in micronucleus tests; sodium pyrithione is therefore not regarded as genotoxic. Sodium pyrithione did not induce carcinogenic effects in 2 oral carcinogenicity studies in rats and in a study in mice with dermal application. For this reason, sodium pyrithione has not been classified in one of the carcinogenicity categories.

Absorption through the skin. After dermal application of sodium pyrithione to rats for 13 weeks at a dose of 15 mg/kg body weight, damage to the muscles and paralysis of the hind legs were observed. The NOAEL was 5 mg/kg body weight (Olin 1988 b; see also Greim 1998). On the basis of an in vivo study in rats, dermal absorption was calculated to be 2 mg after exposure for 10 minutes. A higher level of absorption is to be expected after the standard exposure period of 1 hour.

At a respiratory volume of 10 m^3 and 100% absorption by inhalation, the systemically tolerable amount for exposure at the level of the MAK value is 2 mg. Therefore, the amount absorbed through the skin by rats after 10 minutes is as high as the systemically tolerable amount for humans after 8 hours. The systemic NOAEL for rats after repeated epicutaneous application is very low at 5 mg/kg body weight. Overall, this confirms the "H" designation for sodium pyrithione (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. There are very few findings relating to the contact sensitizing effects induced by sodium pyrithione; similar to the findings for zinc pyrithione, these show that pyrithione salts do not induce marked contact allergenic effects. Negative or borderline results were obtained by maximization tests in guinea pigs; these are not unambiguous.

No clinical findings relating to photocontact sensitizing effects are available in humans and unclear results were determined under experimental conditions. At best, the only conclusion that can be drawn from these findings is that this type of effect may occur. There are no data available for sensitizing effects on the respiratory tract. Therefore, sodium pyrithione is not designated with "Sh" or "Sa" (for substances which cause sensitization of the skin or airways) or with "S(P)" (for substances which cause photocontact sensitization).

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (www.dfg.de/mak/conflicts_interest) ensure that the content and conclusions of the publication are strictly science-based.

References

Barratt MD, Brown KR (1985) Photochemical binding of photoallergens to human serum albumin: a simple in vitro method for screening potential photoallergens. Toxicol Lett 24(1): 1–6. https://doi.org/10.1016/0378-4274(85)90131-6

de Boer EM, van Ketel WG, Bruynzeel DP (1989) Dermatoses in metal workers. (II). Allergic contact dermatitis. Contact Dermatitis 20(4): 280–286. https://doi.org/10.1111/j.1600-0536.1989.tb03146.x

Capitanio JP, Emborg ME (2008) Contributions of non-human primates to neuroscience research. Lancet 371(9618): 1126–1135. https://doi.org/10.1016/S0140-6736(08)60489-4

le Coz C-J (2001) Allergic contact dermatitis from sodium pyrithione in metalworking fluid. Contact Dermatitis 45(1): 58–59. https://doi.org/10.1034/j.1600-0536.2001.045001058.x

ECHA (European Chemicals Agency) (2016) Pyridine-2-thiol 1-oxide, sodium salt (CAS Number 3811-73-2). Registration dossier. Joint submission, first publication 16 Mar 2011, last modification 20 Apr 2016. https://echa.europa.eu/de/registration-dossier/-/registered-dossier/20845, accessed 02 Feb 2017

Geier J, Lessmann H, Dickel H, Frosch PJ, Koch P, Becker D, Jappe U, Aberer W, Schnuch A, Uter W (2004) Patch test results with the metalworking fluid series of the German Contact Dermatitis Research Group (DKG). Contact Dermatitis 51(3): 118–130. https://doi.org/10.1111/j.0105-1873.2004.00416.x

Geier J, Lessmann H, Becker D, Bruze M, Frosch PJ, Fuchs T, Jappe U, Koch P, Pföhler C, Skudlik C (2006) Patch testing with components of water-based metalworking fluids: results of a multicentre study with a second series. Contact Dermatitis 55(6): 322–329. https://doi.org/10.1111/j.1600-0536.2006.00993.x

Geier J, Lessmann H, Skudlik C, Weisshaar E, Schnuch A (2013) Kontaktallergie gegen Bestandteile von Kühlschmierstoffen. IVDK-Daten der Jahre 2005 – 2009. Dermatol Beruf Umwelt 61(4): 137–149. https://doi.org/10.5414/DBX00218

Gerberick GF, Ryan CA (1990) A predictive mouse ear-swelling model for investigating topical photoallergy. Food Chem Toxicol 28(5): 361–368. https://doi.org/10.1016/0278-6915(90)90110-9

Goossens A (2016) Cosmetic contact allergens. Cosmetics 3(1): 5. https://doi.org/10.3390/cosmetics3010005

Greim H, editor (1998) Sodium pyrithione. MAK Value Documentation, 1994. In: Occupational Toxicants. Volume 10. Weinheim: Wiley-VCH. p. 287–311. Also available from https://doi.org/10.1002/3527600418.mb381173kske0010

Greim H, editor (2001) Natriumpyrithion. In: Gesundheitsschädliche Arbeitsstoffe, Toxikologisch-arbeitsmedizinische Begründung von MAK-Werten. 33rd issue. Weinheim: Wiley-VCH. Also available from https://doi.org/10.1002/3527600418.mb381173kskd0033

Gruvberger B, Isaksson M, Frick M, Pontén ANN, Bruze M (2003) Occupational dermatoses in a metalworking plant. Contact Dermatitis 48(2): 80–86. https://doi.org/10.1034/j.1600-0536.2003.480205.x

Hartwig A, editor (2012 a) Natriumpyrithion. In: Gesundheitsschädliche Arbeitsstoffe, Toxikologisch-arbeitsmedizinische Begründung von MAK-Werten. 52nd issue. Weinheim: Wiley-VCH. Also available from https://doi.org/10.1002/3527600418.mb381173kskd0052

Hartwig A, editor (2012 b) Zinkpyrithion. In: Gesundheitsschädliche Arbeitsstoffe, Toxikologisch-arbeitsmedizinische Begründung von MAK-Werten. 52nd issue. Weinheim: Wiley-VCH. Also available from https://doi.org/10.1002/3527600418.mb1346341d0052

Isaksson M (2002) Delayed diagnosis of occupational contact dermatitis from sodium pyrithione in a metalworking fluid. Contact Dermatitis 47(4): 248–249. https://doi.org/10.1034/j.1600-0536.2002.470420_1.x

Kaidbey K (1991) The evaluation of photoallergic contact sensitizers in humans. In: Marzulli FN, Maibach HI, editors. Dermatotoxicology, 4th ed. New York, NY: Hemisphere Publishing Corporation. p. 595–605

Kaidbey KH, Kligman AM (1980) Photomaximization test for identifying photoallergic contact sensitizers. Contact Dermatitis 6(3): 161–169. https://doi.org/10.1111/j.1600-0536.1980.tb05590.x

Kligman AM, Kaidbey KH (1982) Human models for identification of photosensitizing chemicals. J Natl Cancer Inst 69(1): 269–272. https://doi.org/10.1093/jnci/69.1.269

Knox RJ, Keen KL, Luchansky L, Terasawa E, Freyer H, Barbee SJ, Kaczmarek LK (2008) Comparative effects of sodium pyrithione evoked intracellular calcium elevation in rodent and primate ventral horn motor neurons. Biochem Biophys Res Commun 366(1): 48–53. https://doi.org/10.1016/j.bbrc.2007.11.083

Maguire HC, Kaidbey K (1982) Experimental photoallergic contact dermatitis: a mouse model. J Invest Dermatol 79(3): 147–152. https://doi.org/10.1111/1523-1747.ep12500044

OECD (Organization for Economic Co-operation and Development) (2005) Manual for investigation of HPV chemicals. Chapter 3: data evaluation. Paris: OECD. https://www.oecd.org/chemicalsafety/risk-assessment/36045203.pdf, accessed 23 Mar 2015

Olin (1988 a) 4 week oral toxicity study in cynomolgus monkeys. International Research and Development Corporation. Study No. 397-046, 1988, New Haven, CT: Olin Corporation, unpublished

Olin (1988 b) Sodium omadine 90 day dermal toxicity study in the rat. Toxicol Laboratories Limited. Project ID OLA/5/88, 1988, New Haven, CT: Olin Corporation, unpublished

Olin (1988 c) Sodium omadine 90 day oral (gavage) toxicity study in the rat. Toxicol Laboratories Limited. Project ID OLA/2/88, 1988, New Haven, CT: Olin Corporation, unpublished

Olin (1989 a) One year oral toxicity study in cynomolgus monkeys. International Research and Development Corporation. Study No. 397-047, 1989, New Haven, CT: Olin Corporation, unpublished

Olin (1989 b) Sodium omadine rat two-generation reproduction toxicity study. Toxicol Laboratories Limited. Project ID OLA/9/88, 1989, New Haven, CT: Olin Corporation, unpublished

Olin (1989 c) Thirteen week subchronic inhalation toxicity study on Na omadine in rats. International Research and Development Corporation. Study No. 397-042, 1989, New Haven, CT: Olin Corporation, unpublished

Olin (1991 a) Sodium omadine 80 week dermal carcinogenicity study in the mouse. Toxicol Laboratories Limited. Project ID OLA/7/90, 1991, New Haven, CT: Olin Corporation, unpublished

Olin (1991 b) Sodium omadine 104 week oral (gavage) combined carcinogenicity and toxicity study in the rat. Toxicol Laboratories Limited. Project ID OLA/3/90, 1991, New Haven, CT: Olin Corporation, unpublished

Olin (1995) Letter from Olin Corp to USEPA regarding primary eye irritation/corrosion study of 2-pyridinethiol-1-oxide, sodium salt powder in rabbits dated 072794. NTIS/OTS0556316. Alexandria, VA: NTIS. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0556316.xhtml, accessed 02 Feb 2017

Olin (1996) Primary eye irritation/corrosion in rabbits. MB Research Laboratories, Inc. 1996, New Haven, CT: Olin Corporation, unpublished

Olin (1997) Primary eye irritation study in cynomolgus monkeys. WIL Research Laboratories, Inc. 1997, New Haven, CT: Olin Corporation, unpublished

Olin (1998) Primary eye irritation/corrosion in rabbits. MB Research Laboratories, Inc. 1998, New Haven, CT: Olin Corporation, unpublished

Rütgers Chemicals (2004) Natrium Pyrion combined chronic toxicity/carcinogenicity study in rats. RTC Research Toxicology Center. Study No. 7403, 2004, Mannheim: Rütgers Chemicals AG, unpublished

Rütgers Organics (2001 a) "Natrium Pyrion": acute dermal irritation/corrosion study with rabbits. ARC Seibersdorf Research GmbH. 2001, Mannheim: Rütgers Organics GmbH, unpublished

Rütgers Organics (2001 b) "Natrium Pyrion": acute dermal toxicity study with rats. ARC Seibersdorf Research GmbH. 2001, Mannheim: Rütgers Organics GmbH, unpublished

Rütgers Organics (2002 a) Natrium Pyrion chromosome aberrations in Chinese hamster V79 cells in vitro. RTC Research Toxicology Center. Study No. 8108, 2002, Mannheim: Rütgers Organics GmbH, unpublished

Rütgers Organics (2002 b) Natrium Pyrion gene mutation in Chinese hamster V79 cells. RTC Research Toxicology Center. Study No. 8109, 2002, Mannheim: Rütgers Organics GmbH, unpublished

Rütgers Organics (2002 c) "Natrium Pyrion": micronucleus test with mice. ARC Seibersdorf Research GmbH. 2002, Mannheim: Rütgers Organics GmbH, unpublished

Rütgers Organics (2002 d) Natrium Pyrion oral prenatal developmental toxicity study in rats. RTC Research Toxicology Center. Study No. 7404, 2002, Mannheim: Rütgers Organics GmbH, unpublished

Rütgers Organics (2002 e) Natrium Pyrion reverse mutation in Salmonella typhimurium. RTC Research Toxicology Center. Study No. 8107-M-08701, 2002, Mannheim: Rütgers Organics GmbH, unpublished

Rütgers Organics (2002 f) "Natrium Pyrion": skin sensitization study (guinea pig maximization test). ARC Seibersdorf Research GmbH. ARC-UL-0331, 2002, Mannheim: Rütgers Organics GmbH, unpublished

Rütgers Organics (2003) Natrium Pyrion reproduction and fertility study in rats. RTC Research Toxicology Center. Study No. 7406, 2003, Mannheim: Rütgers Organics GmbH, unpublished

Schnuch A, Geier J, Uter W, Frosch PJ (1998) Patch testing with preservatives, antimicrobials and industrial biocides. Results from a multicentre study. Br J Dermatol 138(3): 467–476. https://doi.org/10.1046/j.1365-2133.1998.02126.x

Uter W, Schaller S, Bahmer F, Brasch J, Diepgen TL, Enders F, Frosch PJ, Fuchs T, Henseler T, Muller S, Peters KP, Przybilla B, Schaller J, Schnuch A, Schulze-Dirks A, Stary A (1993) Contact allergy in metal workers – a one-year analysis based on data collected by the "Information Network of Dermatological Clinics" (IVDK) in Germany. Derm Beruf Umwelt 41(6): 220–227

Weyl (1996) Sodium pyrithion: acute oral toxicity test in the rat. Safepharm Laboratories Limited. SPL project number 369/047, 1996, Mannheim: Weyl GmbH, unpublished

Weyl (1997) Sodium pyrithion: ninety day sub-chronic oral (gavage) toxicity study in the rat with neuro-toxicity functional observation battery. Safepharm Laboratories Limited. SPL project number 369/051, 1997, Mannheim: Weyl GmbH, unpublished