Phosphorus

MAK value (2006)	**white/yellow phosphorus:**
	0.05 mg/m³ I
	red phosphorus: not yet established, see Section IIb of the *List of MAK and BAT Values*
Peak limitation (2006)	**white/yellow phosphorus: Category II, excursion factor 2**
	red phosphorus: –
Absorption through the skin	**–**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (2006)	**white/yellow phosphorus: Pregnancy Risk Group C**
	red phosphorus: –
Germ cell mutagenicity	**–**
BAT value	**–**
Synonyms	phosphorus
	white phosphorus (tetraphosphorus)
	yellow phosphorus (tetraphosphorus)
	red phosphorus

Chemical name	phosphorus		
	white phosphorus	yellow phosphorus	red phosphorus
Molecular formula	P_4	P_4	P_n
CAS number	7723-14-0 12185-10-3	7723-14-0 12185-10-3	7723-14-0
Molecular weight	123.895	123.895	n × 30.97

The MAK-Collection Part I, MAK Value Documentations 2015
DFG, Deutsche Forschungsgemeinschaft

Chemical name	phosphorus		
Melting point (°C)	44.1 (ATSDR 1997; ECB 2000)	44.1 (ATSDR 1997; ECB 2000)	≥ 590 (ECB 2000)
Boiling point at 1013 hPa (°C)	280 (ATSDR 1997)	282 (ECB 2000)	> 400 (ECB 2000)
Log K_{OW}[1)]	3.08 (ATSDR 1997)		
Solubility in water at 25°C (mg/l)	4.1 (ECB 2000)		

The reader is to note that a revised MAK supplement appeared in German in 2012. The English version will appear shortly.

The previous MAK value of 0.1 mg/m³ for white and yellow phosphorus was established in 1980 under the name of tetraphosphorus and was based on the then existing TLV (Threshold Limit Value). The current documentation is based on summaries of toxicological data (ACGIH 2001; ATSDR 1997; Commission of Life Sciences 1999; ECB 2000). Elemental phosphorus is present as four allotropes i.e. white or yellow, red, black and violet forms, each with different atomic arrangements. The last two have no relevance to workplace conditions (Beliles 1981), therefore this documentation deals with white (yellow) and red phosphorus. White phosphorus frequently has a yellowish colour, produced by small quantities of red phosphorus, which is the reason why this form is also called yellow phosphorus. This documentation will make no differentiation between white and yellow phosphorus, so that the term "white phosphorus" may apply to either form.

Owing to its great affinity to oxygen, phosphorus is not found free in nature, but only in form of derivates of phosphoric acid. In damp air white phosphorus principally oxidizes to form acids in the oxidation stages: P_2O_3 (phosphonic acid H_3PO_3), P_2O_4 (hypodiphosphoric acid $H_4P_2O_6$) and P_2O_5 (phosphoric acid H_3PO_4) (Holleman and Wiberg 1985).

No studies involving exposure to so-called "phosphorus smoke" are considered in this documentation, as phosphorus pentoxides and its phosphoric acid are formed by the combustion and subsequent burning of highly reactive white phosphorus in a sufficient air (or oxygen) supply (Holleman and Wiberg 1985). As documentations are available for phosphorus pentoxide and phosphoric acid (see documentation "Diphosphorpentaoxid" 2006, only available in German, and documentation "ortho-Phosphorsäure" 2006, only available in German), only those studies will be described below in which white, yellow or red phosphorus are used in solid or dust form.

Phosphorus is used in the production of explosives, smoke bombs, chemicals, rodenticides, phosphorus bronze and fertilizers. Among others, it is an intermediate

1) *n* octanol/water partition coefficient

or by-product in the manufacture of phosphate fertilizers. For this purpose, rocks containing apatite (tricalcium phosphate) are heated and elemental phosphorus released in vapour form (Beliles 1981).

1 Toxic Effects and Mode of Action

When ingested, white phosphorus is rapidly absorbed and efficiently distributed throughout the organism with its highest concentrations in liver, kidney, blood, gastrointestinal tract and skeletal muscle.

White phosphorus is irritating to the skin and mucous membranes of the digestive and respiratory tracts. There are no reliable data on irritation in the eyes. According to available data, which is however insufficiently documented, it seems that red phosphorus has no irritant effects on skin or eyes.

Acute intake of white phosphorus affects the liver, kidneys, haematopoietic system, brain, digestive and circulatory systems as well as the myocardium, producing electrocardiographic changes. Necrosis of the jaw is a known sequel of chronic exposure to white phosphorus at the workplace. The lethal oral dose of white phosphorus in humans is 2 mg/kg body weight.

Increased mortality in pregnant rats and reduced body weight in male rats occurred in studies after repeated oral administration of white phosphorus at a dose of 0.075 mg/kg body weight and day. Loss of hair was also observed. Histopathologically, the male and female rats, as well as their offspring, were without pathological findings in all dose groups. White phosphorus was not mutagenic in a *Salmonella* mutagenicity test. No further in vitro and in vivo studies on genotoxicity are available. Studies on carcinogenicity and sensitization of white phosphorus are also not available.

Red phosphorus had no mutagenic effects in bacteria or yeasts. A Rec-Assay with E. coli was also negative. With the exception of acute inhalation and oral studies, no further useful data are available for red phosphorus.

2 Mechanism of Action

Liver toxicity observed after the ingestion of white phosphorus in the form of fatty degeneration and fibrosis is attributed to damage of the rough and smooth endoplasmic reticulum and disaggregation of the polyribosomes. This initially produces impairment in protein synthesis, more precisely: a decrease in the synthesis of the apolipoprotein portion of VLDL (very low density lipoproteins). As these lipoproteins are necessary for transporting triglycerides, an accumulation of triglycerides in the liver results (ATSDR 1997).

Phosphorus influences bone growth, apparently by decreasing the absorption of intercellular calcified cartilage matrix by osteoclasts in the metaphyseal region of growing bones, which has the long-term effect of slowing down growth (ATSDR 1997).

The pathogenesis of necrosis of the jaw ("phossy jaw") is not clear to date. The most accepted theory assumes that inhaled phosphorus particles react directly with tissue and flora of the mouth. The oral mucous membrane of exposed workers is described as being dull, red and unhealthy in appearance, which is possibly a sequel of the irritant effects of white phosphorus. After such a contact, there is initially a loss of teeth and delayed healing in the dental sockets, followed by necrosis of the jaw accompanied by severe pains and infections (ATSDR 1997; US EPA 1990). It is furthermore conceivable that an accumulation of non-physiological anions (phosphonate and hypodiphosphate ions, see above) in the apatite layer of the bones destroys their hardness.

It is not known whether systemic availability contributes to the development of necrosis of the jaw after the inhalation of white phosphorus. Treatment consists of repeated removal of destroyed bone tissue and teeth, draining of abscesses and applying reconstructive surgery. Even in cases diagnosed very early on, and in which treatment was rapidly initiated, healing often took a number of years. The loss of teeth in late stages of necrosis of the jaw can clearly be attributed to a destruction of the bone structure. It remains unclarified whether a loss of teeth in the early stages or before diagnosis of necrosis of the jaw is clearly attributable to exposure to white phosphorus, or whether poor dental hygiene is the reason for it, as a number of case reports describe very bad dental hygiene in those affected (ATSDR 1997).

3 Toxicokinetics and metabolism

3.1 Absorption, distribution, elimination

White phosphorus is absorbed via the respiratory and the gastrointestinal tract. In rats, the highest concentrations were found five days after oral administration in the liver, skeletal muscles, gastrointestinal tract, blood and kidneys (Beliles 1981). The distribution of radioactivity in the animals' tissue not only remained unchanged after a single oral dose of ^{32}P-labelled white phosphorus, but also remained so after treatment on five consecutive days. The greatest amount of radioactivity was measured in the liver (ATSDR 1997).

Rats, rabbits and mice showed no differences in the distribution pattern 48 hours after single oral administration of ^{32}P-labelled white phosphorus. By means of qualitative and quantitative autoradiography, the greatest amounts of radioactivity were found in the bowel mucosa and in decreasing sequence in the liver, kidneys, spleen, lung, heart, muscle, pancreas and adrenal glands. Radioactivity was also measured in the brain, thymus, thyroid gland, testes, ovaries, uterus, fat, bone, aorta, trachea and pituitary. A greater amount of radioactivity was found in the cortex than in the medulla of the kidneys and the adrenal glands. In the liver, the centrilobular region showed greater uptake compared with other liver areas (ATSDR 1997).

After inhalation of ^{32}P (no other details), the following distribution pattern was found in animals (no other details): lung > bone > liver > kidney. Concentrations in the soft parts decreased rapidly after the end of exposure, however, clearance from the bone took place very slowly. A considerable quantity of ^{32}P could also be found in the skin and hair. The results after inhalation and oral uptake of ^{32}P were comparable (ACGIH 2001).

Elimination is mainly with the urine, mostly in the form of organic and inorganic phosphates (Beliles 1981). The faeces (Chretien 1945; Cushman and Alexander 1966; Diaz Rivera et al. 1950), and exhaled air play roles in the elimination process (Fletcher and Galambos 1963).

Using a saturated aqueous solution as basis, a dermal flux of 0.0002 mg/cm^2/hour can be calculated based on the models of Guy and Potts (1993) and Wilschut et al. (1995) for white phosphorus. This would correspond to a total uptake of 0.4 mg after exposure of both hands and forearms (about 2000 cm^2) for one hour.

Red phosphorus is insoluble, non-volatile and not absorbable (Gosselin et al. 1984).

3.2 Metabolism

No special metabolism studies are available for phosphorus.

In the body, phosphorus is converted to phosphates. Orthophosphate is a stable end product of inorganic oxidation and the hydrolysis of white phosphorus. Although it is possible to determine serum phosphate levels after exposure to white phosphorus, conclusions on the absorbed quantity are, however, not always possible. In an epidemiological study, the mean serum phosphate concentrations of five workers at a phosphorus plant were compared with those of five non-exposed, healthy men. Exposure lasted for up to 17 years. It is assumed that the workers were mainly exposed to airborne phosphorus particles via inhalation, although ingestion by swallowing was also conceivable. The serum phosphate concentrations in exposed and control persons showed no statistically significant differences and were below the normal range for adults (3.0–4.5 mg/100 ml). The serum phosphate concentration in a worker with necrosis of the jaw was also within the normal range. There is no one pattern of human serum concentrations after ingestion, because affected persons frequently vomited after intake or a stomach lavage was performed. In 25 cases of poisoning, concentrations totaled between 1.2–8.6 mg/100 ml from three hours to 36 days after admission. In twelve of the cases sufficient data was reported to calculate oral doses, which were between 7.1 and 22.9 mg/kg body weight and day. Serum phosphate concentrations were within the normal range (4.0–7.0 mg/100 ml serum) in ten children who had either accidentally ingested white phosphorus or had been treated with phosphorus for prevention of rickets (ATSDR 1997).

After applying white phosphorus at concentrations of 26–200 mg/kg body weight to anaesthetized rats using inguinal incisions, burns developed. Serum phosphate concentrations were between 100% and 120% above those of controls 72 hours after application. White phosphorus at a dose of 5700 mg/kg body weight was applied to the intact skin of anaesthetized rabbits. Those animals that died from their burns showed a significant increase in serum phosphate concentrations compared with the concentrations prior to burning, which were between 4.5 and 5.5 mg/100 ml. Between twelve hours and three days after exposure, these were between 6.5 and 10.5 mg/100 ml. The concentrations in the surviving animals remained normal throughout the study (ATSDR 1997).

The activity of microsomal glucose-6-phosphatase in the liver of male Wistar rats increased significantly by 29% or 39% compared with that of controls 12 and 24 hours after acute oral administration. Four hours after administration, no difference was found (ATSDR 1997).

4 Effects in Humans

4.1 Single exposures

There are no studies available on the intake of phosphorus through inhalation.

Studies reporting acute oral exposure to white phosphorus are limited to case reports of intentional or accidental ingestion of match heads, rat and cockroach poison, firecrackers or as a result of military operations. According to descriptions given by the manufacturers of rat poison containing phosphorus, white phosphorus is the only active ingredient. It is also likely that white phosphorus is the agent responsible for the toxicity of cockroach insecticide, match heads and fireworks, although the presence of other toxic compounds cannot be excluded (ATSDR 1997).

The target organs of acute poisoning by white phosphorus are liver, kidneys, brain, digestive system, cardiovascular and haematopoietic systems as well as the myocardium, which produces changes in the electrocardiogram (US EPA 1990). The observations in poisoned persons have been confirmed in acute animal studies (see Section 5.1).

Lethal phosphorus poisoning after ingestion usually involves three stages: symptoms in the first stage include vomiting as well as severe abdominal cramps and pain. In the second stage, the patient improves symptomatically and appears to be recovering. The third stage consists of a rapid decline in the patient's condition with death resulting from organ failure such as the liver, kidneys, cardiovascular or central nervous systems (ATSDR 1997). However, there are also considerable number of cases in which poisoning does not follow the classical three-stage progression (McCarron et al. 1981). Many case reports exist on death following acute ingestion of white phosphorus, though usually without a possible reconstruction of the in-

gested dose, as high doses of the substance may rapidly produce vomiting. Only in one case, that of a woman who had taken about 3.9 g of a rat poison containing 4% white phosphorus, was it possible to reconstruct the dose taken. This is because she did not vomit until two days after intake, so that only a small amount of the absorbed phosphorus was eliminated. The calculated dose was 2 mg/kg body weight and day. The patient died four days after ingesting the rat poison. The cause of death is not reported, autopsy revealed fatty degeneration and cell transformation in the liver (ATSDR 1997).

There were 590 cases of poisoning registered after the intake of white phosphorus combined with potassium chlorate in Ecuador between 1980 and 1999, which were analyzed in a retrospective epidemiological study. The ingested amount of phosphorus varied between 0.3 and 2 g. Ten % of the poisoned persons died. The liver was the most frequently affected organ, followed by the kidneys. The damage to these two organs then resulted in cardiac failure and death (González Andrade et al. 2002).

After skin contact with white phosphorus, injured persons often suffer from second and third degree burns, which may result in death depending on the size of the surface area involved. In these burn victims, effects on the haematopoetic system as well as liver and kidneys were observed (ATSDR 1997).

4.2 Repeated exposures

Necrosis of the jaw frequently occurs in workers exposed to phosphorus particles in the air after long-term exposure. With one exception, all cases of necrosis of the jaw occurred in persons exposed to phosphorus-containing smoke/vapour or dust at the workplace. As white phosphorus oxidizes rapidly in air, the fact that the workers were not only exposed to phosphorus, but also to phosphoric acid and phosphorus oxides cannot be excluded (ATSDR 1997).

In one study, a total of 71 workers at three plants producing fireworks were investigated. Of these, 44 were employed between 15 and 364 days, and 27 for longer than a year. They were continuously exposed to white phosphorus particles in the air. No data are available on exposure levels. In addition, both dermal exposure from processing a phosphorus-containing paste (4–6% white phosphorus) and possibly also oral uptake owing to insufficient hygiene played a role, especially as the sanitary installations were inadequate. The swallowing of phosphorus particles inhaled from the ambient air is conceivable. Some of the workers (number not given) reported an irritant cough. Of the 44 workers exposed for a maximum of one year, two developed a mild necrosis of the lower jaw which took up to two years to heal. Thirteen of the 27 chronically exposed workers developed mild to severe necrosis of the lower or upper jaw. Of these, two female workers died of complications. Septicaemia was diagnosed as the cause of death (ATSDR 1997). Beside anaemia and leukopenia, decreased serum glucose concentrations were also found in the in-

vestigated workers. In another workplace study, no changes in haemoglobin or in total or differential leukocyte levels were observed (no other details; ATSDR 1997).

A 30-year-old man had staged in a magician's act, in which he placed small pellets of phosphorus in his right mucobuccal cavity, for 15 years. After about 14.5 years, the premolar teeth in his right upper jaw became loose and fell out, followed by an absence of healing and the formation of fistulae. Necrosis of the jaw typical for exposure to white phosphorus developed, with massive necrosis of the maxilla and the floor of the right antrum. The upper jaw and nasal cavity became visible due to perforation. No effects were observed on the left side of the maxilla and or of the mandible. In addition, radiography revealed no evidence of pathology in the chest and long bones. A slight decrease in haemoglobin level and an increase in eosinophil level were also found (ATSDR 1997).

There is evidence indicating that exposure to white phosphorus at the workplace damages more than maxillary bones, suggesting a systemic effect for inhaled phosphorus. Two men occupationally exposed to white phosphorus for 20 to 30 years broke their femurs in accidents not normally expected to result in breakage of bones. Examination of bone from the fingertip of one of the workers showed an increased relative proportion of phosphoric acid to lime by nearly 1%. The authors of the review suggest that exposure to white phosphorus may change the bone composition, thereby decreasing the ability of the bone to resist fracture. The data provided by this report, however, is insufficient to definitely attribute the observed effects to occupational exposure to phosphorus (ATSDR 1997).

Several studies are reporting repeated oral administration of white phosphorus to children, in most cases for the treatment of rickets and in some cases as a preventive measure. No deaths occurred in children receiving oral treatment with white phosphorus at doses between 0.026 and 0.158 mg/kg body weight and day for up to 26 months. In most of the children investigated, the long bones showed bands of increased density and an increased thickness and density in the zones of calcification. In one child, there was a decreased gain in body height (from about 0.1 to 0.04 cm per day). However, the authors of the review express their reservation to the effect that "radiological densities" are common at the growing points of long bones in children. In addition, they draw attention to the fact that treatment with white phosphorus did not generally improve the condition of the bones of children suffering from rickets. They point out that the effects observed in these particular children cannot necessarily be transferred to healthy children (ATSDR 1997).

4.3 Local effects on skin and mucous membranes

In the study with 71 pyrotechnical workers already described in Section 4.2 above, the majority of those exposed reported an occurrence of irritant cough. No data on the exposure level to white phosphorus and other components are given (no other details; ATSDR 1997).

As regards the irritant effect of white phosphorus, only a few well-documented original data in an occupational medical context are available. Existing studies are from an earlier date, so that data on exposure level and observed effects are uncertain (ATSDR 1997). In earlier publications on occupational diseases and hygiene, no further data on irritation in the affected workers is found in descriptions of occupational phosphorus poisoning through chronic inhalation of phosphorus vapours, with the exception of an occasional tendency to mucous membrane haemorrhage (no other details) (Baader 1960; Eibel et al. 1931; Koelsch 1946). Ingestion of relatively high doses is consistently made responsible for irritant effects in the gastrointestinal tract (ATSDR 1997).

No studies are available on the effects of white phosphorus on unburned skin in humans. Many of the burns resulting from skin contact with white phosphorus are of second and third degree. It is assumed that skin damage is not only produced by heat but also by the corrosive effect of phosphoric acid and the hygroscopic properties of phosphorus pentoxide. Both are oxidation products of white phosphorus. Severe burns from white phosphorus heal very much more slowly compared with third degree heat burns (ATSDR 1997).

4.4 Allergenic effects

There are no data available.

4.5 Reproductive toxicity

The uterus of a woman two months pregnant who had taken a lethal dose of 2 mg white phosphorus/kg body weight contained a haemorrhagic mole, which was consistent with a two-month pregnancy (ATSDR 1997).

Towards the end of the 19th century, women frequently attempted to induce abortions by ingesting match heads containing phosphorus. Many of these affected died of acute phosphorus poisoning (Nilsson 1995).

No epidemiological investigations on the effects of white phosphorus on fertility and pregnancy are available in the field of human medicine.

4.6 Genotoxicity

There are no data available.

4.7 Carcinogenicity

There are no data available.

4.8 Other effects

Only a few indications allude to the immune system as a target organ for phosphorus. For example, haemorrhage in the thymus was observed in two children who had swallowed fireworks containing phosphorus. These children showed hyperplasia of the abdominal lymphatic tissue, lymph nodes and splenic lymphoid corpuscles. In many persons poisoned by ingestion of rat poison or fireworks containing phosphorus, the leukocyte count was decreased. Both an increase and a decrease in the percentage of neutrophils were observed in persons who had swallowed white phosphorus (ATSDR 1997).

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

There are no studies available on acute toxicity after inhalation of white phosphorus.

The one-hour LC_{50} for red phosphorus in the rat is 4.3 mg/l (4300 mg/m^3). Five of 30 animals (rats and rabbits) died after exposure to 0.68 mg red phosphorus/l (680 mg/m^3) for 30 minutes. Two of ten rats died after inhalation of 1.5 mg/l (1500 mg/m^3) for four hours (ECB 2000).

5.1.2 Ingestion

The oral LD_{50} values for white phosphorus are given as 3.03 mg/kg body weight in female rats and 3.76 mg/kg in male rats. Three of ten rats died after receiving 6 mg/kg body weight by gavage. The LD_{50} is 4.82 mg/kg body weight in female mice and 4.85 mg/kg body weight in males. Six of 17 mice died within three days after admin-

istration of white phosphorus at 6 mg/kg body weight. Red phosphorus is found to be considerably less toxic. Its LD_{50} is given as 15 000 mg/kg body weight in the rat (ATSDR 1997; ECB 2000).

In animal studies, the following liver effects were found after acute exposure: increase in AST (aspartate aminotransferase) and ALT (alanine aminotransferase) levels, impaired liver function, increased liver weight, increased liver triglyceride concentrations, decreased protein synthesis, degeneration of polyribosomes, fatty degeneration and necrosis. The LOAEL for liver effects from white phosphorus is 6 mg/kg body weight in rats, 5 mg/kg body weight in mice, and 0.2 mg/kg body weight in dogs. The liver effects occurred shortly after receiving the dose. There was a significant decrease in protein synthesis in the liver already three hours after administration minimal hepatocytic fatty changes were present after four hours and severe hepatocytic fatty changes were observed after twelve hours. Fatty infiltration in the nephron and subcapsular haemorrhages were observed in dogs after acute exposure (no other details; ATSDR 1997).

Young, growing rabbits received single oral treatment in the form of white phosphorus pills at 0.3 mg /kg body weight and day. Compared with a control group, the metaphyseal regions of tibia and fibula revealed bands of increased density (no other details). The percentage of calcium and phosphorus and the calcium to phosphorus ratio in the metaphyseal and cortical regions of the right tibia found in the animals were similar between treated and control groups (ATSDR 1997).

5.1.3 Dermal absorption

As regards the acute dermal toxicity of white phosphorus, an LD_{50} of about 100 mg/kg body weight is given for the rat (ECB 2000). Certainly, the corrosive effects on the skin are here too decisive for its lethal toxicity.

Three studies in rats are available on the acute dermal toxicity of white phosphorus. Doses of 29, 100 or about 182 mg/kg body weight caused death in 5 of 10, 4 of 8 and 16 of 16 animals. No animals died in the control groups. Information regarding the type of application are lacking. Even though detailed information is absent, these publications are included in the review under those studies in which damage occurred to the animals' skin. Severe liver and kidney damage was found in the animals treated with phosphorus. Histopathology revealed necrosis, degeneration of the hepatocytes as well as microthrombi in the portal veins of the liver, and necrosis, vascular degeneration of the proximal tubules and ischaemic changes in the glomeruli of the kidneys. In addition to the histopathological effects, an increase in ALT activity, increased urea nitrogen level in the blood, excessive diuresis, oliguria and decreased creatinine clearance was observed. The cause of death was probably due to acute renal or hepatic failure (ATSDR 1997).

Studies in rabbits have shown that sufficient quantities of yellow phosphorus are absorbed from burned skin areas, which cause alterations in the electrocardiogram

and sudden, pronounced phosphorus-calcium electrolyte disturbances (ACGIH 2001).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

Rats were exposed to phosphorus vapour (no other details) 7 hours per day for 5 days. Inhalation of more than 20 ppm produced severe irritation of the respiratory tract and a high mortality rate, mainly caused by pulmonary oedema and pneumonia. The formation of hyaline membranes led the authors to assume that the mode of action was the same as that of inhaled mineral fibres (no other details). Exposure of "animals" (presumably rats) to yellow phosphorus at 13–16 ml/m^3 for 7 hours per day on 5 days per week for a period of four months had no effect on body weight gain. This extended exposure produced bone changes and severe damage to liver and kidneys in the animals (ACGIH 2001).

Rats were exposed for 14 months to the atmosphere of a phosphorus factory containing white phosphorus and its inorganic compounds (no other details). Monthly histological investigations revealed progressive morphological degeneration of the tongue and oral mucosa of the cheek, gum and hard palate. Already one month after starting exposure, changes in the epithelial layer were observed, including increases in keratinization and numbers of cell layers resulting in thickening and hyperkeratosis in the epithelium of the mucosa. Over time, the thickening and hyperkeratosis in the epithelium increased and histological changes in the subepithelial connective tissue were found. Eventually, areas were found in the oral cavity in which the mucous membrane was thickened, interspersed with areas with decreased thickness of the mucosa as a result of atrophy, dystrophy and cellular necrosis. The permeability of the capillary walls in the oral cavity was increased, lesions in the vascular walls had developed, and there was evidence of impaired microcirculation. The authors of the review suggest that these effects are not systemic, but most likely the result of direct contact of white phosphorus with the oral cavity. Data on exposure level are lacking (ATSDR 1997).

5.2.2 Ingestion

In two one-generation studies conducted independently of each other by the Monsanto Chemical Company (1983) and Monsanto Chemical Company 1991 a (carried out in year 1989, reported in 1991) using 15 male and 30 female Sprague Dawley rats per group, 30–43% or 53% (16/30) of the pregnant animals treated with white phosphorus by gavage at 0.075 mg/kg body weight for 145 or 204 days (two matings) were either moribund or died during late gestation or birth. In the study with the longer treatment duration, no treatment-related cases of death were found

in the low dose groups treated with 0.005 or 0.015 mg/kg body weight. All of the male rats in the high dose group also survived treatment. Tremor occurred in the animals who did not survive this dose level. In the male rats of the high dose group, the mean body weight was slightly decreased from the fifteenth week compared with controls. Body weight was also decreased in the two lower dose groups, though these differences were neither significant nor dose-dependent. Loss of hair on the forepaw occurred in the high dose group. Histopathological investigation of male and female rats and their offspring revealed no significant effects. Examination also included bones and liver. In the study with the shorter treatment duration, mild to moderate liver necrosis was found in the deceased pregnant animals. There was no such effect in the male rats and the surviving females. In the second study, no liver effects were found in the deceased female animals. The same exposure protocol and the same vehicle (corn oil) were used in both studies. The reason for the differences in the occurrence of liver damage is not clear. The systemic NOAEL for the parent animals is 0.015 mg/kg body weight and day (see Section 5.5.1 and Section 5.5.2; Monsanto Chemical Company 1991 a, b; US EPA 1989). Great care was taken to ensure that oxidation of the white phosphorus did not occur in preparing the test solutions. It is therefore to be expected that white phosphorus really had been administered to these animals.

Rats treated with white phosphorus for their entire life (on average about 420 days) at doses of 0, 0.2, 0.4, 0.8 or 1.6 mg/kg body weight and day with their diet, showed no treatment-related, microscopically visible changes in the lung, although there were bone changes in the form of a thickened epiphysis and greater extension of trabeculae into the diaphysis. Mortality decreased with decreasing dose level, whereby the number of deaths in the lower dose groups was below that of the control group (no other details) (ATSDR 1997; US EPA 1993). This study is inadequate in many ways, for example by the failure to specify incidences of effects during the study, as well as by the failure to state the exact duration of the dosing.

The following liver effects were observed in animals treated orally with white phosphorus: fatty infiltration at 0.75 mg/kg body weight and day for 35 weeks (2 or 4 times per week) in guinea pigs; eosinophilic granules at 0.25 mg/kg body weight and day and cirrhosis at 0.66 mg/kg body weight and day in rabbits and guinea pigs; and fibrosis and cirrhosis at 0.6 mg/kg body weight on 5 days a week for either 12 or 16 weeks in pigs. No liver effects were observed in the pigs until after four weeks; after eight weeks, early signs of fibrosis occurred which had developed into extensive fibrosis after twelve weeks of treatment (ATSDR 1997).

In young growing animals, effects on bone growth were found after treatment with phosphorus: a pill containing 0.6 mg white phosphorus (corresponding to 0.3 mg/kg body weight and day) was administered to young rabbits daily for an intermediate duration (13–117 days). The treated animals showed a reduced growth of the tibial diaphysis by 0.27 mm per day compared with 0.36 mm per day in control animals. Statistical evaluations are not available. Histological abnormalities of the tibia were found in one animal (ATSDR 1997; US EPA 1990). Compared with a control group, weanling Wistar rats also showed histological changes in the

tibia after receiving 1.25 mg/kg body weight and day white phosphorus with their feed for 16 days. The effects observed were possibly caused by a decreased bone resorption during bone growth. This results either in reduced tibial growth or in widening of trabeculae and a denser metaphysis (ATSDR 1997).

Red phosphorus is not toxic after single oral doses. However, repeated doses can result in systemic phosphorus poisoning (no other details; Gosselin et al. 1984).

5.2.3 Subcutaneous injection

Repeated subcutaneous injection of yellow phosphorus at 0.05 mg/kg body weight (total dose of 50 mg) produced bone changes in rats. A NOAEL cannot be derived as this was the lowest tested dose (no other details; ACGIH 2001).

Acute liver necrosis was induced in dogs (mongrels, 23–24 kg body weight) by subcutaneous injections of yellow phosphorus. The animals were injected with 1 mg/kg body weight on two subsequent days and 0.5 mg/kg body weight on the third day. Histological examinations revealed extensive liver necrosis in all dogs, whereas no marked changes were found in the renal parenchyma (Horak et al. 1979).

Female dogs received subcutaneous injections of yellow phosphorus at 0.1, 0.2 or 0.4 mg/kg body weight and day for up to 115 days. All three animals in the highest dose group died within three days. Liver and kidneys were severely damaged. In the 0.2 mg/kg body weight group, liver damage was found in one animal. In five animals of the lowest dose group, haemosiderin deposits and enlargement of the spleen as well as slight changes in kidneys and liver were found (no other details; ECB 2000).

5.3 Local effects on skin and mucous membranes

White phosphorus is designated as being corrosive (no other details). In contrast, red phosphorus was not irritating in the rabbit in a patch test lasting 24 hours (ECB 2000). Data on whether application was occlusive or not are lacking.

In acute dermal toxicity tests, skin necrosis occurred in rats whose skin had been treated with white phosphorus at 29 or 100 mg/kg body weight. Healing of the wounds was delayed in the higher dose group (ATSDR 1997).

White phosphorus in peanut oil was applied to the intact, shaved skin of rabbits (no other details). A 0.1% solution produced no irritation. The same solution was tested in rabbit eyes. Here too, no positive reaction occurred. The authors of the review point out that an irritating effect should have occurred as white phosphorus is highly reactive. In this case, they assume that the peanut oil used as a vehicle protected the animals against this effect (ATSDR 1997).

100 mg red phosphorus was not irritating in the rabbit eye (no other details; ECB 2000).

5.4 Allergenic effects

There are no data available for white phosphorus.

In an investigation with guinea pigs (not described in any greater detail), red phosphorus showed no sensitizing effect (ECB 2000).

5.5 Reproductive toxicity

5.5.1 Fertility

In a study carried out in 1983, groups of 15 male and 30 female Sprague Dawley rats were given white phosphorus dissolved in corn oil at doses of 0, 0.005, 0.015 or 0.075 mg/kg body weight and day by gavage. Treatment started 80 days before mating, continued during mating, pregnancy and lactation periods. As fertility in the first litter (F_{1a}) was too low, the dams were allowed to give birth to a second litter (F_{1b}). Treatment continued up to weaning of the F_{1b} generation, in total 204 days. In the high dose group 16 dams died, 13 of them due to difficulties in giving birth to the F_{1a} or F_{1b} offspring on days 21 or 22 of pregnancy. In the remaining dams of this group, there was a slight but non-significant decrease in the number of live offspring in the F_{1a} litters, accompanied by a slight increase in stillborn offspring. The litters of the F_{1b} generation showed the same trend (see Section 5.2.2; US EPA 1989). The NOAEL for fertility is 0.015 mg/kg body weight and day.

In a study carried out in 1989 with white phosphorus, groups of 15 male and 30 female CD rats were treated with 0.075 mg/kg body weight and day by gavage 11 weeks prior to mating and throughout the mating period. In addition, treatment of the female animals continued up to the end of the lactation period, a total of 145 days. Corn oil was used as vehicle in one group, and tricaprylin (glycerin tricaprylate) in the other. In a further group, the female animals did not receive white phosphorus dissolved in corn oil up to the end of the lactation period, but only up to day 15 of pregnancy. Control groups were treated with corn oil and tricaprylin during the same period. Also in this study, high mortality occurred in the dams treated with white phosphorus (between 30.0% and 42.9%) in all three groups, particularly during the late phase of pregnancy and at birth. The surviving dams were normal. The offspring showed no indications of a disturbed physical development or a reduced survival rate during the lactation period (see Section 5.2.2; Monsanto Chemical Company 1991 a, b (carried out in year 1989, reported in 1991). In both studies, strict care was taken to avoid oxidation of the white phosphorus in preparing the test solutions.

No histological changes in the ovaries, uteri, testes or epididymides were observed in either study (Monsanto Chemical Company 1991 a, b; US EPA 1989).

5.5.2 Developmental toxicity

In a developmental toxicity study, yellow phosphorus dissolved in corn oil was administered by gavage to groups of 25 pregnant Sprague Dawley rats at doses of 0, 0.1, 0.3, 0.6 or 0.75 mg/kg body weight and day from gestation days 6 to 19. In the 0.75 mg/kg group, 21 dams (84%) died. The body weight of the surviving dams was decreased. The foetuses of this dose group were not investigated. Administration of 0.6 mg/kg body weight and day also led to a decrease in body weight gain and death in the dams. There were no indications of an embryotoxic or teratogenic effect of yellow phosphorus in the rats of the 0.6, 0.3 and 0.1 mg/kg groups (Monsanto Chemical Company 1983). In this study, the NOAEL for developmental toxicity is 0.6 mg/kg body weight, corresponding to 3.5 mg/m^3.

In the one-generation study in rats already described in Section 5.2.2 and Section 5.5.1, 0.075 mg/kg body weight and day (0.5 mg/m^3), a maternally lethal dose, produced lethality also in the offspring of the surviving dams. On the other hand, 0.005 and 0.015 mg/kg body weight and day showed no indications of a maternally toxic and embryotoxic effect of white phosphorus (US EPA 1989). The NOAEL obtained from this one-generation study on maternal and developmental toxicity was 0.015 mg/kg body weight and day (0.1 mg/m^3). This markedly lower NOAEL in comparison with the developmental toxicity study can be attributed to the longer duration of administration.

5.6 Genotoxicity

White phosphorus in water ("phossy water") was negative both in the presence and absence of a metabolic activation system in a bacterial mutagenicity test using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 at 100 µl/plate. Cytotoxicity occurred at 1 µl/plate in strain TA1535, and at 10 µl/plate in the remaining strains (US EPA 1990).

The same strains were also tested with red phosphorus up to 10 mg/plate. No mutagenic effect was found either in the presence or absence of a metabolic activation system. Using red phosphorus at 10 mg/plate, a differential killing test with *Escherichia coli* and a test for mitotic recombination with *Saccharomyces cerevisiae* were also negative (no other details; US EPA 1990).

5.7 Carcinogenicity

No studies with carcinogenicity as endpoint are available for assessment.

In a study published in 1942, in which six rats per group were treated with white phosphorus in peanut oil at 0, 0.2, 0.4, 0.8 or 1.6 mg/kg body weight and day for their entire lifetime (average duration: 420 days) with their diet, no treatment-re-

lated histopathological lesions were observed in the lungs or other organs up to the highest dose; bone changes (not specified in greater detail) were the exception (see Section 5.2.2; ATSDR 1997; US EPA 1990).

Groups of six to ten male and female rats were treated by subcutaneous injections of elementary phosphorus in vegetable oil at doses between 0.5 and 3.2 mg/kg body weight and day twice a week for their entire lifetime. A control group was injected with the vehicle. The average survival duration was between 3.2 and 610 days. No treatment-related lesions occurred. This study, which was not designed as a carcinogenicity study, has a number of limitations, in particular due to the small group size. The maximum tolerated dose was not reached (no other details; US EPA 1990, 1993).

5.8 Other effects

There are no data available.

6 Manifesto (MAK value, classification)

White/Yellow phosphorus:

White phosphorus frequently has a yellow shade, produced by slight quantities of red phosphorus. This form is also called yellow phosphorus. In this section, no differentiation is made between white and yellow phosphorus; the term "white phosphorus" is used for both forms.

White phosphorus is highly irritating in the respiratory tract. Although no data on its irritant effect to the eyes are available, it is assumed to have strong irritant effects in this case as well.

No animal studies or reports on effects in humans are available from which a MAK value for white phosphorus from inhalation can be derived. Details on exposure level are lacking in those workplace studies describing an irritant effect. They are therefore not suitable for establishing a MAK value.

The NOAEL for systemic toxicity after oral administration of white phosphorus for 204 days to rats in a one-generation study with two matings is 0.015 mg/kg body weight and day. Already at 0.075 mg/kg body weight and day, increased mortality in the dams and a significantly lower body weight in the male animals were found.

The NOAEL of 0.015 mg/kg body weight and day would correspond to a concentration at 0.105 mg/m^3 in humans assuming a respiratory volume of 10 m^3, a body weight of 70 kg and retention of 100%. Based on this systemic NOAEL, the MAK value for white/yellow phosphorus is reduced to 0.05 mg/m^3. Due to the reactivity of phosphorus in air, it is possible that a phosphorus oxide layer on the outer surface forms larger particles, while a core made up of elementary phosphorus remains (von Stackleberg et al. 2004). The irritant effect of the finely distributed phosphorus

is therefore due to contact with phosphorus pentoxide or, in humid air, to contact with the acids (see Introduction). The MAK values for phosphorus pentoxides and phosphoric acid are 2 mg/m³ I and are based on an inhalation study in rats exposed to an aerosol consisting of the combustion products of red phosphorus/butyl rubber (95:5). It is assumed that, due to its reactivity in air, the major part of the phosphorus contained in the aerosol is initially converted by combustion to phosphorus pentoxide, of which an unknown amount is in turn converted to phosphoric acid on contact with air humidity and most certainly quantitatively on inhalation. In the study, the animals' noses were also investigated and no effects were found (see documentation "Diphosphorpentaoxid" 2006, only available in German, and documentation "ortho-Phosphorsäure" 2006, only available in German). At the MAK value of 0.05 mg/m³ I for white phosphorus, no irritant effects are therefore to be expected. The amounts of phosphorus and phosphorus pentoxides occurring after exposure to phosphorus are not known, for which reason care must be taken in every case that the MAK value for phosphorus pentoxides is also observed. As the critical effect is the systemic effect, white phosphorus is reclassified in Peak Limitation Category II. No data are available from which a substance-specific excursion factor could be derived. An excursion factor of 2 is therefore established. From the reasons described above, an irritant effect is also not to be expected at the permissible peak concentrations then in effect.

Due to its burning and corrosive effects, no longer-term contact between white phosphorus and the intact skin is possible. Owing to the poor water solubility of phosphorus, the theoretically calculated quantities for penetration through the intact skin are also very low. For these reasons white phosphorus is not designated with an "H".

No data on sensitizing effects of white phosphorus are available. Therefore, it is not designated with "Sh" or "Sa".

In 1992, white phosphorus was classified in Pregnancy Risk Group D under the term "tetraphosphorus", as corresponding investigations in a second species were not available. An oral developmental toxicity study in rats revealed a NOAEL of 0.6 mg/kg body weight, corresponding to 3.5 mg/m³. The difference between this and the MAK value of 0.05 mg/m³ is sufficient to classify the substance in Pregnancy Risk Group C. In a one-generation study, toxic effects in the offspring were found at relatively low doses of 0.075 mg/kg body weight and day, corresponding to 0.5 mg/m³ which were, however, highly toxic or lethal for the pregnant dams. Neither maternal toxicity nor embryotoxicity occurred at doses of 0.015 mg/kg body weight (0.1 mg/m³). Since when one avoids maternal toxicity, no developmental toxicity is observed at the same time, the substance is therefore classified in Pregnancy Risk Group C.

In the *Salmonella* mutagenicity test, white phosphorus was not mutagenic. As no further data on genotoxicity and no investigations on the carcinogenicity useful for assessment are available, white phosphorus is not classified in one of the categories either for carcinogens or for germ cell mutagens.

Red phosphorus:

The irritant effect of red phosphorus seems to be slight, though no valid studies on the subject are available. There are no inhalation studies in either humans or animals from which a MAK value could be derived. Red phosphorus is therefore listed in Section IIb of the *List of MAK and BAT Values*.

According to the present state of knowledge, red phosphorus is not irritating to the skin, and it cannot be absorbed either. For this reason, red phosphorus is not designated with an "H".

No evaluable studies on the sensitizing effects of red phosphorus are available. Therefore, it is not designated with "Sh" or "Sa".

Red phosphorus had no mutagenic effects in bacteria or yeasts. The results of a Rec-Assay with *Escherichia coli* were also negative. No other investigations on the genotoxicity of red phosphorus in vitro or in vivo are available. Studies on its carcinogenicity are also not available. For this reason it is not classified in one of the categories either for carcinogens or for germ cell mutagens.

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