

PROPHAM

First draft prepared by J.-J. Larsen
National Food Agency, Ministry of Health
Søborg, Denmark

EXPLANATION

Propham, isopropyl carbanilate, is the active substance of several products used as herbicides and potato sprout inhibitors. It was previously evaluated by the JMPR in 1963 and 1965 (Annex 1, references 2 and 3) at which time the data available were considered inadequate for allocating an ADI.

EVALUATION FOR ACCEPTABLE DAILY INTAKE**BIOLOGICAL DATA****Biochemical aspects****Absorption, distribution, and excretion**

The tissue distribution and excretion of ^{14}C -labelled propham (purity > 99%, specific activity of chain-labelled molecule 4.9 mCi/mmol and of ring-labelled molecule 4.1 mCi/mmol) were investigated in adult female Wistar rats (mean body-weight 270 g). A single oral dose (2 animals per dose) of 0, 0.67, 19, 38, or 75 mg/kg bw ^{14}C -labelled propham ($5\mu\text{Ci}$ in 1.0 ml of 20% aqueous ethanol solution) was administered by intubation. Rats were housed individually in glass metabolism cages; expired air was continuously monitored for radioactivity for 72 h. The faeces and urine samples were collected at 24, 48, and 72 h and analyzed for ^{14}C by liquid scintillation counting. The urine was analyzed by paper chromatography and thin-layer chromatography. In a similar experiment, single rats were killed at various times (1-24 h) after administration of a single dose of 0.81 mg/kg bw ^{14}C -labelled propham/kg bw ($5\mu\text{Ci}$ in 1.0 ml of a 20% aqueous ethanol solution). Tissue samples (kidneys, liver, blood, lungs, heart, spleen, intestine, brain, muscle, and fat) were freeze-dried, and analyzed for ^{14}C by gas-flow G-M counter.

The average 3-day excretion of radioactivity in urine, faeces, and CO_2 was 80, 5, and 5%, respectively after chain-labelling of propham, and 85, 5, and 0%, respectively after ring-labelling of propham. There was no significant difference in the rate of excretion or the route of elimination among rats receiving different dosages. The radioactivity was distributed in all examined tissues with the highest

concentrations in the kidneys. The average biological half-life of propham in most organs was short, ranging between 3 and 8 h. However, in brain, fat, and muscle, the half-life was about twice the value for other organs. Propham was metabolized by hydrolytic and oxidative mechanisms and the resulting metabolites were excreted either as free forms or as conjugates. Tentative identification of the metabolites indicated the following substances to be present in urine: (4-OH)-propham, 1-OH-2-propyl-propham, 1-carboxyl-1-ethyl-propham, and (4-OH)-propham-sulphate (Fang *et al.*, 1974).

Biotransformation

The metabolic fate of propham was investigated in male Wistar rats weighing approximately 250 g. The animals received a single dose of 15 mg ¹⁴C-labelled propham (purity 98.8%) intraperitoneally in 0.2 ml absolute ethanol (n=5) or orally as a suspension in 1.0 ml syrup (n=6). Urine, faeces and carbon dioxide were collected for up to 4 days after dosing, the respired gases being trapped in 20% sodium hydroxide solution. For biliary studies, bile was collected for 6 h after injection of 0.5 mg ¹⁴C-labelled propham in 0.25 ml 40% aqueous ethanol into the femoral vein of rats under urethane anaesthesia. Other rats received 50 mg neomycin sulphate in 0.5 ml water orally 24 h before an oral dose of ¹⁴C-labelled propham. The drinking-water provided for these animals contained 1% neomycin sulphate. Radioactivity was measured by liquid scintillation counting.

After both oral and intraperitoneal doses approximately 80% of the administered radioactivity appeared in the urine over 4 days, with much smaller amounts appearing in the faeces and respired air. Of the urinary radioactivity about 80% was present as the sulphate ester of isopropyl N-(4-hydroxyphenyl)carbamate. Little or no isopropyl N-(2-hydroxyphenyl)-carbamate was formed. Neomycin feeding studies suggested that the small amount of hydrolysis which occurred was mediated by the animal rather than by its gut microflora. Biliary elimination of ¹⁴C-labelled propham was also examined, about 30% of an intravenous dose being excreted in the bile within 6 h (Bend *et al.*, 1971).

The identification of propham metabolites was studied in six male Sprague-Dawley rats, weighing 220-274 g, and a lactating goat weighing 48 kg. Each animal was given a single dose by stomach tube of 100 mg/kg bw ¹⁴C-ring-labelled propham (purity 99%, 6.8-8.6 μ Ci in the rats and 37 μ Ci in the goat, specific activity not given). Faeces and urine (plus milk from the goat) were collected separately at 6, 24, and 48 h after dosing. The samples were analyzed together with fractions from the liver, heart, kidneys, intestine, intestinal content, and the remaining carcass for ¹⁴C by liquid scintillation techniques.

Radioactivity was rapidly eliminated in the urine of both the rat and goat during the first 6 h after dosing. The cumulative 48-h excretion of radioactivity, in per cent of the dose given, in urine was 96% and 90% in the rat and goat,

respectively, and in faeces 2% and 3% in rat and goat, respectively. Radioactivity in milk was highest during the first 6 h after dosing. The cumulative 48-h milk radioactivity was 0.45% of the dose. The content of radioactivity 48 h after dosing was highest in the liver. The relative content of radioactivity of the heart, kidney, and intestine seemed to be quite different in rat and goat. The data indicated that biliary excretion of propham metabolites into the intestinal tract had occurred. The metabolites in the rat included: glucuronic acid conjugate of isopropyl 4-hydroxycarbanilate, sulphate ester of isopropyl 4-hydroxycarbanilate, sulphate ester of 4-hydroxyacetanilide and several other minor unidentified compounds. Goat urinary metabolites included the sulphate ester of isopropyl 4-hydroxycarbanilate, glucuronic acid conjugate of isopropyl 4-hydroxycarbanilate, another conjugated form of isopropyl 4-hydroxycarbanilate, a conjugate of isopropyl 3,4-dihydroxycarbanilate, the sulphate ester of isopropyl 2-hydroxycarbanilate, a conjugate of 4-hydroxyaniline, the sulphate ester of 2-hydroxyaniline, another conjugated form of 2-hydroxyaniline, the glucuronic acid conjugate of 4-hydroxyacetanilide, a conjugate of (2-hydroxyisopropyl)4-hydroxycarbanilate and several other unidentified compounds (Paulson *et al.*, 1973).

Effects on enzymes and other biochemical parameters

No data available.

Toxicological studies

Acute toxicity studies

Studies of acute toxicity following oral (animals fasted 16 h before dosing) or dermal administration or after inhalation of propham were performed (purity 98.4%) in SPF-bred Wistar rats, Bor strain: WISW (SPF Cpb) (body-weight 160-200 g) and acclimatized and randomised before use (Mihail, 1984; Pauluhn, 1984).

Table 1. Acute toxicity of propham

Species	Strain	Sex	Route	LD ₅₀ mg/kg bw	LC ₅₀ mg/l	Reference
Rat	Wistar	M	oral	4300		Mihail (1984)
	Wistar	F	oral	8700		
Rat	Wistar	M	dermal	> 5000		Mihail (1984)
	Wistar	F	dermal	> 5000		
Rat	Wistar	M	inhal.		> 2.1	Pauluhn (1984)
	Wistar	F	inhal.		> 2.1	

Short-term toxicity studies

Four groups of 10 Wistar rats (Bor strain, WISW/SPF Cpb)/sex, 4 to 5 weeks old were fed dietary concentrations of 0, 200, 1000 or 5000 ppm (equal to 0, 14, 70 or 384 mg/kg bw/day for males and 0, 21, 109 or 576 mg/kg bw/day for females) 99.3% purity propham for 13 weeks. Stability and homogeneity in the diet were based on parallel studies (dietary concentrations, 100 and 15 000 ppm), which indicated acceptable results (i.e. $\pm 10\%$ of nominal values). Body-weight, food and water intake were monitored weekly. Haematology, clinical biochemistry, gross pathological examinations and histopathological examinations were performed.

Appearance, behaviour and mortality of the rats were unaffected by dosages of up to 5000 ppm. Food intake of females was slightly increased at all three dose levels, but the increase was not dose-dependent. At 5000 ppm the body-weight gain in males was slightly but statistically significantly reduced. A significant and dose-dependent decrease was seen in the erythrocyte counts, haemoglobin, haematocrit and mean cell haemoglobin concentration and an increase was seen in the mean cell volume in males receiving 1000 and 5000 ppm and in females receiving 5000 ppm. Cholesterol concentrations were increased in females at 5000 ppm. Males dosed with 1000 and 5000 ppm had a significantly increased relative adrenal weight and at 5000 ppm increased relative liver and spleen weights. In females a significant increase in relative liver weight was observed at 1000 ppm and a significant increase in relative kidney and liver weight at 5000 ppm. At 1000 and 5000 ppm a treatment-related effect on liver function (liver weight and ASAT activity) was seen in both sexes. A dose-dependent increase in haemosiderin content in the spleen was seen in both sexes at 1000 and 5000 ppm. Based on the effects on the blood parameters a NOAEL of 200 ppm equal to 14 and 21 mg/kg bw/day in males and females, respectively, was determined (Hahnemann & Vogel, 1984).

Four groups of 20 SPF Wistar rats (Bor strain, WISW/SPF Cpb)/sex, 5 to 6 weeks old and weighing 68 to 124 g (males) or 84 to 116 g (females) were fed dietary concentrations (99.4% purity propham) of 0, 10, 30 or 100 ppm equal to 0, 0.6, 1.8 or 5.8 mg/kg bw/day for males and 0, 0.7, 2.4 or 7.8 mg/kg bw/day for females for 12 months. Homogeneity in the 10 and 100 ppm diet was within $\pm 10\%$ and stability of diets stored under similar conditions to those in the study were within $\pm 3\%$ of original concentrations. Body-weight, food and water intake were monitored weekly up to week 13 and biweekly thereafter. Haematology, clinical biochemistry, urinalysis, and ophthalmoscopy were performed and gross pathological examinations and histopathological examinations were carried out. The body-weight was unaffected in both sexes at all dose levels as were mortality and clinical signs. Haematological data indicated no significant effects at 10 and 30 ppm. At certain times during the treatment with 100 ppm statistically

significantly reduced erythrocyte counts, leucocyte cell counts, per cent lymphocytes in differential blood count and haematocrit were observed. Statistically significantly increased values for mean MCH and MCHC compared to control values were noted. Haemosiderosis in spleen was more severe in the propham-treated males compared to control animals. A NOAEL of 100 ppm, equal to 5.8 or 7.8 mg/kg bw/day for males and females respectively, was determined (Eiben, 1988a).

Long-term toxicity/carcinogenicity studies

Rats

Four groups of 20 SPF Wistar rats (Bor strain, WISW/SPF Cpb)/sex, 4 to 5 weeks old, and weighing 72 to 110 g (males) or 73 to 107 g (females) were fed dietary concentrations (99.3% purity propham) of 0, 100, 500 or 2500 ppm equal to 0, 5.7, 29 or 150 mg/kg bw/day for males and 7.6, 37 or 200 mg/kg bw/day for females, for 24 months. Ten additional rats/sex/dose level were fed similar diets and were sacrificed at 12 months. Homogeneity based on diet containing 100 or 15 000 ppm was within $\pm 10\%$ and stability under conditions of storage similar to those used in the present study indicated 101 to 109% of initial concentrations. Body-weight, food and water intake were monitored weekly up to week 13 and biweekly thereafter. Haematology, clinical biochemistry, urinalysis, and ophthalmoscopy were performed and gross pathological examinations and histopathological examinations were carried out. No treatment-related incidences of clinical signs and symptoms, changes in food and water intake or mortality were observed up to the dosage of 2500 ppm. Body-weight gain was comparable to control rats up to 2500 ppm (males) and 500 ppm (females). At 2500 ppm, weight gain was slightly decreased in females during the second half of the study. No evidence of any treatment-related adverse effects on the blood or haematopoietic organs was found in the 100 ppm dosage group. At and above 500 ppm, evidence of increased haemopoiesis was observed in the spleen and liver. Reduced erythrocyte and haematocrit counts and increased spleen weights were also recorded in the 2500 ppm groups. At 2500 ppm mineralization in the kidneys and increased relative kidney weights were observed most often in the females. No adverse effects were noted for any other organ systems. Ophthalmological investigations revealed age-related eye changes which were fairly evenly distributed over all groups. No carcinogenic potential of propham could be inferred from the type, frequency or time of onset of benign or malignant tumours. Based on the effects on the blood parameters, a NOAEL for propham of 100 ppm, equal to 5.7 and 7.6 mg/kg bw/day in males and females respectively was determined. Carcinogenicity was not demonstrated (Eiben, 1989).

Hamsters

The Meeting determined that the data available in a published carcinogenicity study on golden hamsters (Van Esch & Kroes, 1972) were inadequate to permit evaluation. The authors concluded that there was no

indication of a carcinogenic effect of propham in hamsters at a dose level of 200 mg/kg bw/day given daily for 33 months.

Reproduction studies

In a two-generation, two-litter per generation Wistar rat (Bor strain, WISW/SPF Cpb) reproduction study, 4 groups of 25 rats/sex (initial age 4 to 6 weeks, weighing 62-93 g) were fed diets containing 0, 200, 1000 or 5000 ppm, 99.3-99.4% purity propham, equal to 0, 20, 80 or 100 mg/kg bw/day in the F₀ generation and 0, 20, 100 or 550 mg/kg bw/day in the F₁ generation. Homogeneity and stability were determined in parallel studies for dietary concentrations of 100 and 15 000 ppm. Homogeneity was within $\pm 10\%$ and stability data indicated 101 and 109% of nominal values. F₀ animals were inspected daily for clinical signs and were weighed weekly mating (after approximately 16 weeks on test for F₀ animals and at about 100 days of age for F_{1b} parents) was determined by vaginal smear. Lactation period was 4 weeks. F_{1a}, F_{2a} and F_{2b} pups were sacrificed at weaning and subject to gross and histopathological examination.

At dietary concentrations up to 5000 ppm there were no effects on appearance, behaviour, general condition, mortality, fertility, insemination rate, gestation, viability, duration of pregnancy or sex ratio. No malformations were observed and incidence of stillbirths was unaffected. The lactation index and mean litter size at birth were comparable to those of the controls up to 1000 ppm. At 5000 ppm, the lactation index was in some cases significantly depressed and the litter size was reduced. Body-weight gain was not retarded in the parent animals or in the pups up to 1000 ppm. The body-weight of parents and pups in the 5000 ppm group increased more slowly during the rearing period. Food intake was unaffected up to 1000 ppm. Following 5000 ppm F_{1b} rats consumed less food. The macroscopic examination of the dissected F_{1b} and F_{2b} pups revealed no changes of organs related to the treatment. The histopathological investigations revealed indications of increased breakdown of the red blood cells from 200 ppm upwards in F₀ and F_{1b} parents, which was identified by an increased incidence of siderosis in the liver and/or spleen. At 5000 ppm increased extramedullary haematopoiesis was frequently observed and increased spleen weights were recorded. At 200 ppm and above (F_{1b}) and from 1000 ppm and above (F₀) spleens were commonly dark in colour. No indications of organ damage were found in the other organs of parent animals in the gross pathology examinations nor on the basis of the organ weights or histopathological investigations. In all dosage groups, therefore, signs of increased breakdown of erythrocytes were found. The dose of 200 ppm of propham was therefore toxic to parental animals. Based on effects on lactation index, food intake and body-weight gain, a NOAEL for reproduction of 1000 ppm equal to 80 mg/kg bw/day, was determined. The NOAEL for maternal toxicity (haematological effects) was < 200 ppm (equal to 20 mg/kg bw/day) (Eiben, 1988b).

The effect of propham on the haematopoietic organs was investigated in a 6-month reproduction study in rats, since a NOAEL in this context had not been determined in the previous 2-generation study. Propham (purity 99.1-99.4%) was administered at dietary concentrations of 0, 20, 60 or 180 ppm to F₀ males (25 animals/dosage group) and F₀ females (25 animals/dosage group), their F₁ litters until weaning and for a further 6 months to 20 male and 20 female weaned F₁ rats from these litters. The dosages in the F₁ generation were equal to 0, 1.8, 5.3, or 16 mg/kg bw/day in the males and 0, 2.3, 6.7, or 21 mg/kg bw/day in the females. SPF-bred Wistar rats, Bor strain: WISW (SPF Cpb), were acclimatized before use. All animals were randomized in order to obtain comparable groups. At the start of the study, the rats had an age of 11-16 weeks and a body-weight of 300-349 g (F₀ males) and 189-217 g (F₀ females). Test for homogeneity from a parallel study showed a mean propham concentration of 97%, 90%, and 99% of nominal values in feed containing 20, 100, and 15 000 ppm, respectively. Tests for stability from a parallel study resulted in 105%, 101%, and 109% of nominal values in feed containing 20, 100, and 15 000 ppm, respectively. The animals were inspected daily for general clinical signs and specific behaviours. The body-weight and food intake was recorded weekly during study. Mating was determined by presence of sperm in vaginal smears or by finding of vaginal plugs. The body-weight of each of the F₁ litter was determined weekly and each pup underwent inspections for malformations. Blood samples were taken from 10 animals per group for haematological examination. Organ weights were determined and histopathological examinations were carried out on selected tissues.

Dietary concentrations of 180 ppm propham were tolerated without any adverse effect on general behaviour, mortality or any of the reproduction parameters of the F₀ generation (fertility, gestation, viability, lactation, litter size and litter weight). No malformations or increase in the number of still-births were observed. Feed intake, appearance, behaviour, body-weight gain (lactation period and 6 months treatment period) and mortality of adult F₁ rats remained unaffected at dosages up to 180 ppm. Haematological investigations were negative. No findings were obtained at autopsy which indicated any treatment-related organ damage or changes in organ weights of liver, spleen or kidney. During the histopathological examination of liver, spleen, kidneys and bone marrow, no treatment-related pathological findings were observed up to 180 ppm. Detection of ferruginous pigment in liver, kidney and spleen was within the normal variability.

Administration of 180 ppm propham equal to 16 and 21 mg/kg bw/day in males and females, respectively, was tolerated with no adverse effects during the ante-natal development phase, the rearing period and the following 6 months. NOAELs for reproduction and maternal toxicity exceeded 180 ppm, equal to 16 mg/kg bw/day (Eiben, 1988c).

Special studies on genotoxicity

Data are shown in Table 2.

Table 2. Results of genotoxicity assays on propham

Test system	Test object	Concentration of propham	Purity	Results	Reference
<i>In vitro</i>					
Ames test (with and without metabolic activation)	<i>Salmonella typhimurium</i>	300-4800 µg/plate	99.6%	Negative (+ S9)	Herbold (1992)
Sister chromatid exchange (without metabolic activation)	Human lymphocytes	10 ⁻⁴ , 10 ⁻⁵ , 10 ⁻⁶ M	n.g.	Negative	Lindahl-Kiessling <i>et al.</i> (1989)
Gene mutation (dexamethasone resistance) (without metabolic activation)	S-49 Mouse lymphoma cells	1.1 - 2.2 M	n.g.	Negative	Friedrich & Nass (1983)
<i>In vivo</i>					
Micronucleus test	Mouse (NMRI)	2 x 1000 mg/kg bw and 2 x 2000 mg/kg bw orally. The two doses were administered with an interval of 24 h	99.9%	Negative	Machemer (1977)

n.g. = not given

Special studies on teratogenicity.

Four groups of 25 pregnant Wistar rats (strain, Bor WISW/SPF Cpb) were dosed orally with a 0.5% aqueous suspension of propham at 0, 30, 100 or 300 mg/kg bw/day on days 6-15 of pregnancy. Fetuses were removed by caesarean section on day 20 of pregnancy.

The body weight, clinical signs and pregnancy rate of the dams were unaffected by propham. There were no treatment-related mortalities among the fetuses. Malformations occurred in three fetuses of two dams in the 300 mg/kg bw group and in one fetus of a dam in the 30 mg/kg bw/day group and in none of the control or 100 mg/kg bw/day group. One of the three fetuses had multiple skeletal anomalies and two fetuses had exencephaly and some other malformations. The Meeting concluded that this study was inadequate for evaluation (Renhof, 1984).

Special studies on skin-sensitizing effect

Propham was tested in female guinea-pigs for skin sensitizing properties using Magnusson and Kligman's Maximization Test. SPF-bred DHPW female guinea-pigs were used. The animals were acclimatized for at least 7 days before start of treatment. At the start of treatment the guinea-pigs were 4-7 weeks old and weighed 276-358 g. The animals were observed daily throughout the study for clinical signs and body-weights were recorded before and at the end of study. Propham (purity 99.6%) was formulated in Cremophor EL (2% v/v) in physiological NaCl solution. The stability of propham was satisfactory. An analysis showed that 95-97% of the active substance in the test solution was found after 24 h storage. The homogeneity of test solutions was also satisfactory. The mean content of three samples from each of two test solutions was 93-108% of the nominal values. The test animal group consisted of 10 guinea-pigs, and two control groups consisted of 10 animals each. The following propham concentrations were used: intradermal induction: 2.5%, topical induction: 25%, and challenge: 25%. Following shaving of the backs and flanks of the guinea-pigs three intradermal injections (injection volume 0.1 ml) with a distance of 1-2 cm were given in a row per side to the left and right of the spinal column. Topical induction with propham in cremophor/saline solution was performed one week after intradermal induction. Challenge exposure (0.5 ml) was performed three weeks after intradermal induction. A hypoallergenic dressing soaked in the 25% test article formulation was placed for 24 h on the left flank of propham animals and first control group. A control dressing was placed on the right flank. The criterion for sensitization was a higher incidence and intensity of skin reaction in test animals compared to control animals. All animals tolerated the treatment without signs of toxicity and no skin reactions occurred among the test or control animals. There is thus no indication of a skin sensitizing effect of propham (Diesing, 1989).

Observations in humans

No data available.

COMMENTS

Following oral administration to rats, propham was rapidly eliminated via the urine (80-96%), faeces (5%), and expired air (5%). Metabolism proceeds by hydrolysis and oxidation.

Propham had a low acute oral toxicity in rats. The World Health Organization has classified propham as unlikely to present acute hazard in normal use (WHO, 1992).

In short-term toxicity studies in rats at dietary concentrations of 0, 200, 1000, or 5000 ppm for 13 weeks or of 0, 10, 30, or 100 ppm for 12 months, effects were observed on haematological parameters, ASAT and relative weight of the adrenals, liver and spleen. Increases in haemosiderin content in the spleen were seen. On the basis of the haematological effects the NOAEL was 100 ppm, equal to 5.8 and 7.8 mg/kg bw/day in males and females, respectively.

In a 2-year long-term toxicity/carcinogenicity study in rats at dietary concentrations of 0, 100, 500, or 2500 ppm propham, effects on haematological parameters and spleen weight were observed. Increased haemopoiesis was seen in the spleen and liver. On the basis of the effects on the haematological parameters the NOAEL was 100 ppm, equal to 5.7 and 7.6 mg/kg bw/day in males and females, respectively. There was no evidence of carcinogenicity.

A 33-month study in hamsters was inadequate for evaluation.

In a two-generation reproduction study in rats at dietary concentrations of 0, 200, 1000, or 5000 ppm propham, the NOAEL was 1000 ppm, equal to 80 mg/kg bw/day, on the basis of effects on lactation index, food intake, and body-weight gain.

An oral teratogenicity study in rats was inadequate for evaluation.

Although the data were not fully adequate, the Meeting concluded that propham was not likely to be genotoxic.

The available toxicological data on propham were not adequate to allocate an ADI.

Studies without which the determination of an ADI is impracticable

1. A biotransformation study in rats.
2. Short-term toxicity study in a non-rodent species.
3. A test specifically for aneuploidy.
4. Teratogenicity study in two species.
5. Available observations in humans.

REFERENCES

Bend, J.R., Holder, G.M. & Ryan, A.J. (1971) Further studies on the metabolism of isopropyl N-phenylcarbamate (propham) in the rat. *Fd. Cosmet. Toxicol.*, **9**: 169-177.

Diesing, L. (1989) Studies on skin-sensitizing effect in guinea-pigs. Unpublished report No. 17537 from Institute of Toxicology, Agrochemicals, Department of Toxicology, Bayer AG, Friedrich-Ebert Str. 217-333, D-5600 Wuppertal 1, Germany. Submitted to WHO by Bayer AG, Wuppertal, Germany.

Eiben, R. (1988a) Chronic toxicity study in Wistar rats. Supplementary study to investigate effects on the spleen. Unpublished report No. 17170 from Institute of Toxicology for Industrial Chemicals, Fachbereich Toxicology, Bayer AG, Friedrich-Ebert Str. 217-333, D-5600 Wuppertal 1, Germany. Submitted to WHO by Bayer AG, Friedrich-Ebert Str. 217-333, D-5600 Wuppertal 1, Germany.

Eiben, R. (1988b) Two-generation study in rats. Unpublished report No. 16880 from Institute of Toxicology for Industrial Chemicals, Fachbereich Toxicology, Bayer AG, Friedrich-Ebert Str. 217-333, D-5600 Wuppertal 1, Germany. Submitted to WHO by Bayer AG, Friedrich-Ebert Str. 217-333, D-5600 Wuppertal 1, Germany.

Eiben, R. (1988c) Six month feeding study after intrauterine pretreatment (supplementary study to clarify haemotoxic effects). Unpublished report No. 16877 from Institute of Toxicology for Industrial Chemicals, Fachbereich Toxicology, Bayer AG, Friedrich-Ebert Str. 217-333, D-5600 Wuppertal 1, Germany. Submitted to WHO by Bayer AG, Friedrich-Ebert Str. 217-333, D-5600 Wuppertal 1, Germany.

Eiben, R. (1989) Chronic toxicity and carcinogenicity investigations in Wistar rats. Unpublished report No. 17947 from Institute of Toxicology for Industrial Chemicals, Fachbereich Toxicology, Bayer AG, Friedrich-Ebert Str. 217-333, D-5600 Wuppertal 1, Germany. Submitted to WHO by Bayer AG, Friedrich-Ebert Str. 217-333, D-5600 Wuppertal 1, Germany.

Fang, S.C., Fallin, E., Montgomery, M.L. & Freed, V.H. (1974) Metabolic studies of ¹⁴C-labelled propham and chlorpropham in the female rat. *Pesticide Biochemistry and Physiology*, **4**: 1-11.

Friedrich, U. & Nass, G. (1983) Evaluation of a mutation test using S49 mouse lymphoma cells and monitoring simultaneously the induction of dexamethasone resistance, 6-thioguanine resistance and quabain resistance. *Mutation Research*, **110**: 147-167.

Hahnemann, S. & Vogel, O. (1984) Subchronic toxicity studies in rats (13-week feeding study). Unpublished report No. 13083 from Institute of Toxicology for Industrial Chemicals, Fachbereich Toxicology, Bayer AG, Friedrich-Ebert Str. 217-333, D-5600 Wuppertal 1, Germany. Submitted to WHO by Bayer AG, Friedrich-Ebert-Str. 217-333, D-5600 Wuppertal 1, Germany.

Herbold, B.A. (1992) *Salmonella*/microsome test. Unpublished report No. 21469 from Institute of Toxicology for Industrial Chemicals, Fachbereich Toxicology, Bayer AG, Friedrich-Ebert Str. 217-333, D-5600 Wuppertal 1, Germany. Submitted to WHO by Bayer AG, Friedrich-Ebert-Str. 217-333, D-5600 Wuppertal 1, Germany.

Lindahl-Kiessling, K. Karlberg, I. & Olofsson; A-M. (1989) Induction of sister-chromatid exchanges by direct and indirect mutagens in human lymphocytes, co-cultured with intact rat liver cells. *Mutation Research*, **211**: 77-87.

Machemer, L. (1977) Micronucleus test on the mouse for testing for mutagenic effects. Unpublished report No. 7067 from Institute of Toxicology for Industrial Chemicals, Fachbereich Toxicology, Bayer AG, Friedrich-Ebert Str. 217-333, D-5600 Wuppertal 1, Germany. Submitted to WHO by Bayer AG, Friedrich-Ebert-Str. 217-333, D-5600 Wuppertal 1, Germany.

Mihail, F. (1984) Study for acute oral and dermal toxicity. Unpublished report No. 12577 from Institute of Toxicology for Industrial Chemicals, Fachbereich Toxicology, Bayer AG, Friedrich-Ebert Str. 217-333, D-5600 Wuppertal 1, Germany. Submitted to WHO by Bayer AG, Friedrich-Ebert-Str. 217-333, D-5600 Wuppertal 1, Germany.

Pauluhn, J. (1984) Study for acute inhalation toxicity and irritation/corrosion effect in the rabbit. Unpublished report No. 12633 from Institute of Toxicology for Industrial Chemicals, Fachbereich Toxicology, Bayer AG, Friedrich-Ebert Str. 217-333, D-5600 Wuppertal 1, Germany. Submitted to WHO by Bayer AG, Friedrich-Ebert-Str. 217-333, D-5600 Wuppertal 1, Germany.

Paulson, G.D., Jacobsen, A.M., Zaylskie, R.G. & Feil, V.J. (1973) Isolation and identification of propham (isopropyl carbanilate) metabolites from the rat and the goat. *J. Agr. Food Chem.*, **21**: 804-811.

Renhof, M. (1984). Study for embryotoxic effect on the rat following oral administration. Unpublished report No. 12655 from Institute of Toxicology for Industrial Chemicals, Fachbereich Toxicology, Bayer AG, Friedrich-Ebert Str. 217-333, D-5600 Wuppertal 1, Germany. Submitted to WHO by Bayer AG, Friedrich-Ebert-Str. 217-333, D-5600 Wuppertal 1, Germany.

Van Esch, G.J. Van & Kroes, R. (1972). Long-term toxicity studies of chlorpropham and propham in mice and hamsters. *Fd. Cosmet. Toxicol.*, **10**: 373-381.

WHO (1992) The WHO recommended classification of pesticides by hazard and guidelines to classification 1992-1993 (WHO/PCS/92.14). Available from the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland.