PROPAMOCARB

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Explanation

Propamocarb (propyl-3-(dimethylamino) propylcarbamate) is a carbamate fungicide that was developed for the control of phycomycetous fungi. A toxicological monograph was prepared by the JMPR in 1984 and a monograph addendum was prepared in 1986. In 1986, an acceptable daily intake (ADI) of 0–0.1 mg/kg bw was established based on a no-observed-adverse-effect

level (NOAEL) of 200 ppm, equivalent to 10 mg/kg bw per day, on the basis of minimal non-specific toxicity (i.e. reductions in body weight and food consumption) observed in a 2-year feeding study in rats.

Propamocarb was re-evaluated by the present Meeting within the periodic review programme of the Codex Committee on Pesticide Residues. The Meeting reviewed a substantial amount of new data on propamocarb that had not been considered previously, as well as relevant data from the previous evaluation.

All pivotal studies with propamocarb were certified as being compliant with good laboratory practice (GLP).

Evaluation for acceptable daily intake

1. Biochemical aspects

1.1 Absorption, distribution and excretion

Rats

The kinetics of [^{14}C]propamocarb hydrochloride (propamocarb-HCl) (radiochemical purity, > 98%) was studied in groups of five male and five female Sprague Dawley rats treated by gavage with either a single dose of radiolabelled propamocarb at 10 or 1000 mg/kg bw, or unlabelled propamocarb-HCl at 10 mg/kg bw per day for 14 days followed by a single dose of radiolabelled propamocarb at 10 mg/kg bw on day 15. One group of rats received a single intravenous dose (10 mg/kg bw) of [^{14}C]propamocarb-HCl. Excretion of radioactivity in the urine and faeces was monitored for 2–3 days, after which the animals were killed and tissue concentrations of radioactivity were determined in whole blood, plasma, liver, kidney, spleen, heart, lung, brain, muscle, gonads, eyes, adrenals, bone, renal fat, gastrointestinal tract, thyroid and carcass. Statements of adherence to quality assurance (QA) and GLP were provided.

After a single oral dose of propamocarb-HCl at 10 mg/kg bw, 74–78% of the administered radioactivity was excreted in the urine within 6 h, increasing to 89–91% at 24 h and 92–95% at 48 h. At 48 h, 2–4% was excreted in the faeces and the remaining radioactivity was found predominantly in the liver and lungs.

After a single dose of propamocarb at 1000 mg/kg bw, excretion was somewhat slower, with 21–32% of radioactivity excreted in the urine within 6 h and 75–90% excreted within 24 h. After 72 h, 93–96% of radioactivity was excreted in the urine and 2–5% was excreted in the faeces. At 72 h, tissue concentrations of radioactivity were highest in the adrenals, carcass and liver of both sexes and in kidneys, ovaries, lungs and renal fat of females.

After repeated oral administration, 48–56% of administered radioactivity was excreted in the urine within 6 h, and 75–82% and 78–84% was excreted in the urine at 24 and 48 h respectively. Total excretion of radiolabel in the faeces was 2–4%. At 72 h, radioactivity was predominantly found in the liver in both sexes and in the kidneys in males only.

After a single intravenous dose of propamocarb-HCl at 10 mg/kg bw, 68–77% of radioactivity was excreted in the urine within 6 h. At 24 h, 84–88% of radioactivity was excreted in the urine. Within 72 h, 87–89% was excreted in the urine, while 1–2% was excreted in the faeces. At 72 h, radioactivity was predominantly found in the liver, kidney (male only) and lungs (Reynolds, 1994a).

The rate of clearance of [^{14}C]propamocarb-HCl (radiochemical purity, > 98%) from tissues after single oral (gavage) doses (10 and 1000 mg/kg bw) was studied in Sprague-Dawley rats. In the group receiving the lower dose, the animals (three of each sex) were killed at 0.5, 1, 3, 9, 24 and 48 h after dosing. In the group receiving the higher dose, the rats (three of each sex) were

killed at 0.5, 1, 3, 24, 48 and 72 h after dosing. The concentration of radioactivity in whole blood, plasma, liver, kidney, spleen, heart, lung, brain, muscle, gonads, eyes, adrenals, bone, renal fat, thyroid, gastrointestinal tract and carcass was measured. Statements of adherence to QA and GLP were provided.

In the group receiving the lower dose, the highest concentrations of radioactivity were found 0.5 h after dosing in the gastrointestinal tract, kidney and liver. Radioactivity was cleared rapidly and by 48 h after dosing tissue concentrations had fallen to below 0.4 mg of propamocarb equivalents/kg tissue (with the exception of the gastrointestinal tract).

In the group receiving the higher dose, tissue concentrations peaked mainly after 0.5 h in males and after 1 h in females. At these early time-points, the highest concentrations were found in the gastrointestinal tract, kidney, liver, lungs, and thyroid. Radioactivity concentrations fell rapidly in all tissues. The calculated terminal half-lives for tissues ranged from 11 h to 26 h (O'Boyle, 1994).

The elimination and tissue distribution of radioactivity after administration of [^{14}C]propamocarb-HCl (radiochemical purity, 95.5%) as single oral (gavage) doses at 10 and 1000 mg/kg bw was studied in male Sprague Dawley rats (lower dose, $n = 4$; higher dose, $n = 2$). Urine and faeces were collected at 6, 12, 24, 48 and 72 h after dosing. Statements of adherence to QA and GLP were provided.

Propamocarb was rapidly excreted, with 60% and 38% of the administered radioactivity excreted within the first 6 h, 89% and 92% within 24 h, and 91% and 94% within 72 h in the animals receiving the lower and higher dose, respectively. Most (88–92% at 72 h) of the radiolabel was excreted in the urine. Excretion in the faeces at 72 h was 1.5% and 2.8% of the dose, at the lower and higher dose, respectively. At 72 h, low concentrations of radioactivity were found in tissues. The highest concentrations were found in the liver, kidneys and carcass (Morley & Reynolds, 1997).

The kinetics of [^{14}C]propamocarb-HCl (radiochemical purity, > 98%) was studied after single and multiple administrations to Sprague-Dawley rats in a number of experiments. Statements of adherence to QA and GLP were provided.

In a pilot study, two rats of each sex received a single oral dose at 100 mg/kg bw by gavage. Excretion of radiolabel in urine, faeces and expired air was measured during 96 h. Recovery of radiolabel in males and females was 98% and 101.5%, respectively. The major route of excretion was urine (92% in males, 93% in females). Small amounts were excreted in the faeces (4.5% in males, 6% in females) and expired air (< 0.02%).

In a second pilot study, two rats of each sex received a single oral dose of 100 mg/kg bw by gavage. Blood was sampled from the lateral tail vein at 0.5, 1, 2, 4, 6, 8, 12, 24 and 48 h after dosing. Blood and plasma concentrations of radioactivity peaked at 0.5–1 h, indicating that absorption is rapid. Plasma concentrations fell below detection levels within 12 h, and half-lives of about 2 h were calculated. Elimination from whole blood was slower, with calculated half-lives of about 20 h for males and 17 h for females.

In a subsequent experiment, groups of four male and four female rats received a single oral (gavage) dose at 1 or 100 mg/kg bw. Blood was collected from the tail vein at 0.25, 0.5, 1, 3, 6, 8, 12, 24, 48 and 72 h after dosing. No marked differences in kinetics in the blood between the groups receiving the lower or higher dose, or males and females were observed. Concentrations of radioactivity in plasma and whole blood peaked at 0.5–0.9 h. Plasma and whole blood half-lives ranged from 1.6 to 2.9 h.

Subsequently, groups of four male and four female rats received a single oral (gavage) dose at 1 or 100 mg/kg bw, and urine and faeces samples were collected at 6 (urine only), 12, 24, 36, 48, 72, 96, 120, 144 and 168 h. At termination, concentrations of radioactivity in the carcasses were determined. Elimination of radioactive label was rapid. Within 12 h, excretion of

radioactivity in urine was 86–89% in the group receiving the lower dose and 82–88% in the group receiving the higher dose. During the rest of the period of 168 h, only 8–11% and 8–9% of the administered radioactivity was recovered at the lower and higher dose, respectively. Total excretion of radioactivity in faeces was 4–6% and 3–4% at the lower and higher dose, respectively. Less than 1% of radioactivity was recovered from the carcasses at the lower and higher dose.

In a study of tissue distribution, groups of 12 male and 12 female rats received propamocarb as a single dose at 1 or 100 mg/kg bw by gavage. At 0.75, 3, 6 and 24 h after dosing, three animals of each sex per dose were killed and exsanguinated. Concentrations of radioactivity were determined in a range of organs and tissues. At the lower dose, concentrations had already peaked at 0.75 h in most tissues, with the highest concentrations found in the gastrointestinal tract and organs involved in the elimination of propamocarb, i.e. liver and kidney. At the higher dose, tissue concentrations of radioactivity peaked at 0.75–3 h, with highest concentrations in gastrointestinal tract, adrenals, spleen, kidney and skin. The tissue concentrations for animals in the group at 100 mg/kg bw were approximately 100-fold higher than those found in the group at 1 mg/kg bw. No remarkable differences between males and females were observed.

In a repeated dose experiment, groups of 12 male and 12 female rats received daily oral doses (gavage) of non-radiolabelled propamocarb (1 mg/kg bw per day) on 14 consecutive days, followed by a single oral dose of [^{14}C]propamocarb at 1 mg/kg bw on day 15. At 0.75, 3, 6 and 24 h after dosing, three animals of each sex per dose were killed and exsanguinated. Concentrations of radioactivity in a range of organs and tissues were determined. Similar to the single dose experiment with 1 mg/kg bw, tissue concentrations of radioactivity were at a maximum at 0.75 h, with highest concentrations found in the gastrointestinal tract, liver and kidney.

In general, no remarkable differences between males and females were observed with respect to the absorption, distribution and excretion of propamocarb (Beyerbach & Morrison, 2000).

1.2 Biotransformation

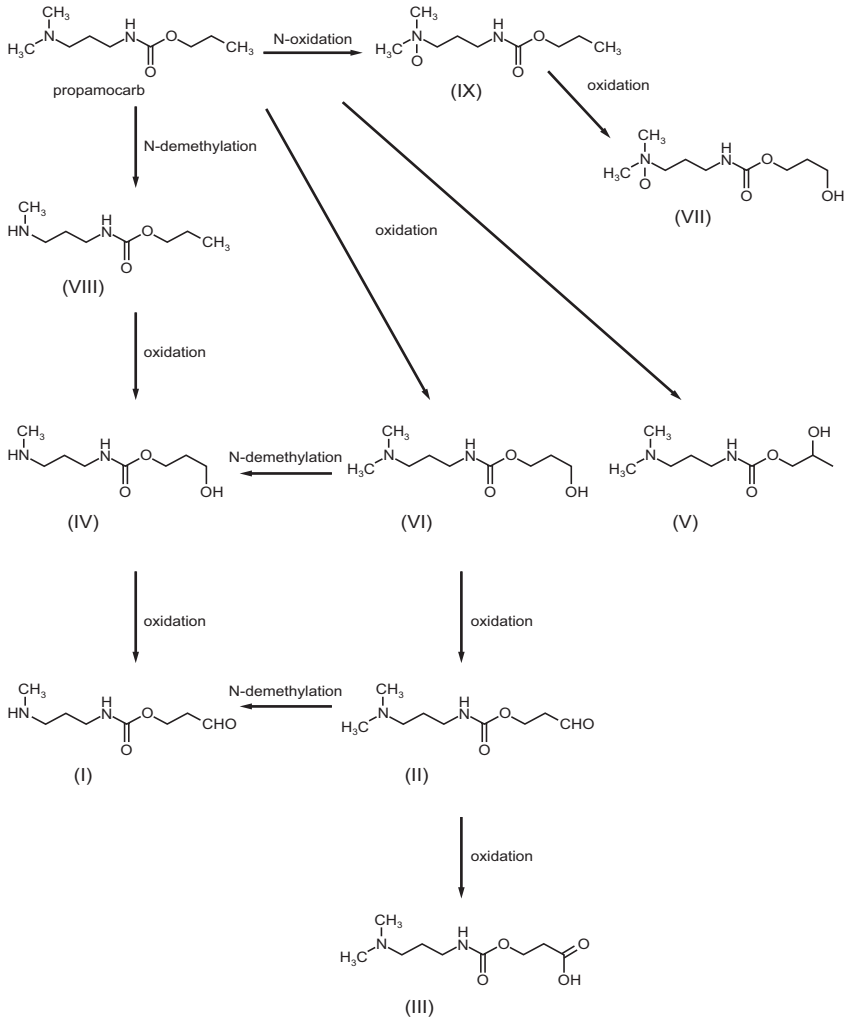
Rats

Biotransformation of propamocarb was studied after single and multiple oral dosing in rats. In the single-dose experiment, groups of four male and four female rats received [^{14}C]propamocarb as a single oral (gavage) dose at 1 or 100 mg/kg bw and urine and faeces were collected over 24 h. In the repeated dose experiment, groups of three male and three female rats received 14 daily oral doses (gavage) of unlabelled propamocarb (1 mg/kg bw per day), followed by [^{14}C]propamocarb as a single oral dose at 1 mg/kg bw on day 15. Urine and faeces were collected over the 24 h after administration of the radiolabelled propamocarb. The urine and faeces samples were analysed for propamocarb and its metabolites. Statements of adherence to QA and GLP were provided.

Excretion occurred predominantly in the urine. Less than 4% of the radiolabel was recovered from the faeces. Propamocarb was extensively metabolized, with the metabolite profiles in the urine and faeces being qualitatively similar in both sexes, at the lower and higher doses, and in the groups given a single or repeated doses. Between four and nine major metabolites were found. The major metabolites of propamocarb in urine were carbonyl propamocarb and hydroxy propamocarb, found at about 25% and 10% at the lower dose (single and repeated dosing), and about 13% and 22% at the higher dose. Propamocarb-*N*-oxide was present at about 3.4% in the group receiving the lower dose (single and repeated dosing) and 12% in the group receiving the higher dose. Unchanged propamocarb was only found in the urine of animals at the higher dose (3% males and 6.7% in females). In the faeces, carbonyl propamocarb, carboxy propamocarb, hydroxy demethyl propamocarb and hydroxy propamocarb were the major metabolites.

Metabolism of propamocarb mainly occurs through oxidation of the propyl chain and *N*-oxidation and *N*-demethylation of the *N*-methyl groups. The proposed pathway is depicted in Figure 1 (Beyerbach & Morrison, 2000).

Figure 1. Proposed metabolic pathway of propamocarb



From Beyerbach & Morrison (2000)

Met I	Mono demethyl carbonyl propamocarb
Met II	Carbonyl propamocarb
Met III	Carboxy propamocarb
Met IV	Hydroxy mono demethyl propamocarb
Met V	2-Hydroxy propamocarb
Met VI	Hydroxy propamocarb
Met VII	Hydroxy propamocarb *N*-oxide
Met VIII	Mono demethyl propamocarb
Met IX	Propamocarb *N*-oxide

In the study of Beyerbach & Morrison (2000), substances accounting for 6–18% of the radioactivity in the urine were not identified. In a subsequent study, further attempts were made to elucidate the structures of these urinary metabolites. The study was performed on the same urine samples as used by Beyerbach & Morrison (2000). Statements of adherence to QA and GLP were provided.

In the urine samples, two more major metabolites were identified: 3-(dimethylamino)propylamine accounted for about 5% of the lower dose administered (i.e. 1 mg/kg bw), and about 3% of the dose at 100 mg/kg bw, and 3-(dimethylamino)propylamine-*N*-oxide accounted for 6–7% of the lower dose administered (i.e. 1 mg/kg), and 3% of the dose at 100 mg/kg. With respect to the proposed pathway (Figure 1), 3-(dimethylamino)propylamine is a further direct transformation product of the parent compound propamocarb, while 3-(dimethylamino)propylamine-*N*-oxide fits in as an hydrolysis product of propamocarb *N*-oxide, which is a *N*-oxide of the parent compound (Beyerbach & Lappin, 2000).

The metabolic profile of [^{14}C]propamocarb-HCl (radiochemical purity, > 98%) was studied in rats (Sprague Dawley) after single oral (gavage) doses (10 or 1000 mg/kg bw) and multiple oral (gavage) doses (daily dose of 10 mg/kg bw of unlabelled propamocarb-HCl for 14 days followed by [^{14}C]propamocarb-HCl at 10 mg/kg bw on day 15). One group of rats received a single intravenous dose (10 mg/kg bw) of [^{14}C]propamocarb-HCl. Urine and faeces were collected for up to 3 days. Urinary metabolites were identified in pooled samples of urine from males and females. Statements of adherence to QA and GLP were provided.

In all groups, most of the radioactivity (78–96%) was excreted in the urine (excluding cage wash). In the faeces, 1–5% of the radiolabel was excreted.

At the lower dose (single or repeated oral dosing and intravenous administration), the metabolic profile of propamocarb was quantitatively and qualitatively similar. In these groups, 3–11% of the administered dose was excreted in urine as unchanged propamocarb in the urine. In the group receiving the higher dose, the amount of unchanged propamocarb excreted in the urine was higher, i.e. 20% of the administered dose. Apart from the parent compound, four major metabolites were identified. These were 2-hydroxypropamocarb at 15–21%; mono demethyl propamocarb (only measured for the group receiving the higher dose owing to inadequate separation from parent compound by high-performance liquid chromatography (HPLC) for the groups receiving the lower dose); propamocarb-*N*-oxide at 9–21%; and 3-(3-dimethylaminopropyl)-4-hydroxy-4-methyloxazolidin-2-one at 17–22% at the lower dose and 3% at the higher dose.

There was no evidence of conjugation with glucuronic or sulfuric acid.

The metabolism involved aliphatic oxidation of the propyl chain (to form 2-hydroxy propamocarb) followed by rearrangement, *N*-oxidation of the tertiary amine (propamocarb *N*-oxide), and *N*-demethylation (mono demethyl propamocarb) (Reynolds, 1994b).

The metabolism of [^{14}C]propamocarb-HCl (radiochemical purity, 95.5%) was studied after single oral (gavage) doses at 10 and 1000 mg/kg bw in male Sprague Dawley rats (lower dose, $n = 4$; higher dose, $n = 2$). Urine was collected for 72 h after dosing. Statements of adherence to QA and GLP were provided.

Metabolite profiles in urine for groups at the lower and higher doses were qualitatively similar. At the lower and higher dose, respectively, 1% and 20% of radioactivity in urine represented the parent compound. At the lower and higher doses the major metabolites and their respective levels were propamocarb *N*-oxide (27% and 10%), 3-(3-dimethylaminopropyl)-4-hydroxy-4-methyloxazolidin-2-one (19% and 33%), 2-hydroxy propamocarb (38% and 24%) and mono demethyl propamocarb (1% and 6%) (Morley & Reynolds, 1997).

2. Toxicological studies

2.1 Acute toxicity

The results of studies of acute toxicity with propamocarb are summarized in Table 1. All studies were performed with formulations (Previcur N, Proplant) containing 66.5–72% propamocarb-HCl.

In studies of acute oral toxicity, clinical signs of toxicity included hypokinesia, lethargy, hunched posture, body tremors, clonic convulsion, nasal haemorrhage, mouth haemorrhage, piloerection, staggering gait and ataxia within 24 h after dosing.

In studies of acute dermal toxicity, no signs of overt toxicity were observed.

In studies of acute toxicity after inhalation, clinical signs included wet fur, hunched posture and piloerection, lethargy, noisy respiration, changed respiratory rate and staining of the fur.

(a) Dermal irritation

In a study of dermal irritation in New Zealand White rabbits, performed in compliance with United States Environmental Protection Agency (USEPA) guideline 81-5, three males and three females were exposed to 0.5 ml of Previcur N (containing 68.7% propamocarb-HCl), under occlusion for 4 h. Irritation was scored according to the Draize method. A statement of adherence to QA was provided.

In all animals, erythema was observed 1 h after removal of the occlusive dressing. The effect was reversed within 24–48 h (Ullman & Suter, 1983b).

Table 1. Acute toxicity with propamocarb

Species	Strain	Sex	Route	LD_{50}[a] (mg/kg bw)	LC_{50}[a] (mg/l air)	Propamocarb-HCl content (%)	Reference
Mouse	ICR	Male	Oral	2650	—	65.5	Kojima et al. (1982a)[b]
		Female		2800			
Rat	Wistar	Male	Oral	2900	—	66.5	Kojima et al. (1982b)[b]
		Female		2000			
Rat	SD	Male	Oral	> 2000	—	71.5	Allen (1995a[c]
		Female		> 2000			
Mouse	ICR	Male & female	Dermal	> 3000	—	66.5	Kojima et al. (1982c)[b]
Rat	Wistar	Male & female	Dermal	> 3000	—	66.5	Kojima et al. (1982d)[b]
Rat	SD	Male & female	Dermal	> 2000	—	71.5	Allen (1995b)[c]
Rat	SD	Male & female	Inhalation (4 h)	—	> 3.60	72.2	Blagden (1995)[c]
Rat	SD	Male & female	Inhalation (4 h)	—	> 5.54	71.2	Blagden (1998)[c]

SD, Sprague-Dawley

[a] The median lethal doses (LD_{50}s) and concentrations (LC_{50}s) are expressed in mg of propamocarb-HCl per kg bw and mg of propamocarb-HCl per litre, respectively.

[b] Statement of adherence to QA was provided.

[c] Statements of adherence to QA and GLP were provided.

In a study of dermal irritation, performed in compliance with Organisation for Economic Co-operation and Development (OECD) guideline 404, six female NZW rabbits were exposed to 0.5 ml of Proplant (containing 72.2% propamocarb-HCl). The test material was applied under a gauze patch for 4 h. Irritation was scored according to the Draize method. Statements of adherence to QA and GLP were provided.

Very slight erythema was observed 1 h after removal of the occlusive dressing. The reactions resolved within 24 h (Allen, 1995c).

(b) Ocular irritation

In a study of ocular irritation in rabbits, which was performed according to USEPA guideline 81-4, three males and three females received 0.1 ml of Previcur N (containing 68.7% propamocarb-HCl) in the left eye. The right eye served as control. A statement of adherence to QA was provided.

The only sign of irritation was slight redness of the conjunctiva, observed in five out of six animals at 24 h. This had reversed by 72 h (Ullman & Suter, 1983a).

In a study of ocular irritation, which was performed according to OECD guideline 405, 0.1 ml of Proplant (containing 72.2% propamocarb-HCl) was applied to the left eye of six female New Zealand White rabbits. Irritation was scored according to the Draize method for 3 days. Statements of adherence to QA and GLP were provided.

Minimal conjunctival redness in one animal at 24 h was the only finding (Allen, 1995d).

(c) Dermal sensitization

In a study of dermal sensitization, which was performed according to OECD guideline 406 and using the Buehler method, 20 female Dunkin Hartley guinea-pigs were given Proplant (containing 71.5% propamocarb). The control group consisted of 10 females. The treatment regime involved induction of sensitization by topical administration on days 0, 2, 4, 7, 9, 11, 14, 16 and 18 and challenge by topical administration on day 28. The test substance was applied undiluted in the induction phase, and undiluted or as a 75% (v/v) solution in distilled water during the challenge phase. Statements of adherence to QA and GLP were provided.

No adverse reactions were noted at the test material sites of the test or control group animals, both during the induction phase and at 24 and 48 h after administration of the challenge dose (Allen, 1995e).

The skin sensitization potential of a propamocarb-HCl liquid concentrate (containing 71.2% propamocarb-HCl) was tested in 20 female Dunkin Hartley guinea-pigs, according to OECD guideline 406 using the Magnusson-Kligman maximization test. Ten animals served as controls. In the induction phase, the animals received propamocarb by intradermal injection (7.5% v/v) on day 1 followed by a topical administration (10% v/v) on day 8 and challenge by topical administration (2.5 and 5% v/v in distilled water) on day 22. Statements of adherence to GLP and QA were provided.

At the intradermal induction site, necrosis was seen in all animals. After topical application in the induction phase slight erythema was observed in all animals. After the challenge dose, 9 out of 20 animals showed dermal reactions, mainly erythema and occasionally oedema, indicating that propamocarb is a skin sensitizer (Coleman, 1999).

2.2 Short-term studies of toxicity

(a) *Oral administration*

Mice

In a 90-day study of toxicity, groups of 10 male and 10 female mice (Crl:CD-1(ICR)BR strain) received diets containing a propamocarb-HCl liquid concentrate (propamocarb-HCl content, 71.2%) at a concentration of 0, 1404, 2808, 5616 or 11232 ppm, corresponding to propamocarb-HCl at 0, 1000, 2000, 4000 or 8000 ppm. These concentrations provided average daily intakes of propamocarb-HCl of 169, 341, 669 and 1349 mg/kg bw for males and 210, 468, 933 and 1952 mg/kg bw for females. The test was performed according to OECD 408. Statements of adherence to QA and GLP were provided.

No treatment-related effects on mortality, clinical signs, body weight, food consumption, ophthalmoscopy, absolute and relative organ weight, macroscopy and histopathology were observed. The NOAEL for propamocarb was 8000 ppm, the highest dose tested, equal to 1349 and 1952 mg/kg bw per day for males and females, respectively (Hubbard, 1998a).

In a 3-month dose range-finding study, groups of five male and five female CD-1 mice received Proplant (containing 75% propamocarb-HCl) at a dose of 0, 10, 30, 100, 300 or 1000 mg of propamocarb-HCl per kg bw per day by gavage. The animals were checked daily for clinical signs. Body weights and food consumption were measured weekly. All animals were necropsied and a wide range of organs and tissues of the animals in the control group and at the highest dose were examined histologically.

No treatment-related effects were observed (Blair, 2001a).

Rats

In a 28-day range-finding study, groups of five male and five female Fischer CDF (F344) Crl:Br rats were fed diets containing Proplant (containing 67% propamocarb-HCl) at a concentration of 0, 2500, 5000, 12 500, 25 000 or 50 000 ppm, equal to propamocarb-HCl at 0, 172, 425, 995, 2047 and 5700 mg/kg bw per day for males and 0, 185, 457, 1055, 2402 and 6430 mg/kg bw per day for females. Animals were checked twice daily for clinical signs. Body weights and food consumption were measured on days 1, 8, 15, 22 and 28. All animals were necropsied and selected organs were weighed.

At the highest dose, one female was found dead on day 15, while the rest of the animals in this group were killed for humane reasons on days 11–15. At lower doses, no animals died. Dose-related clinical signs in males at 25 000 and 50 000 ppm and females at 12 500, 25 000 and 50 000 ppm included decreased activity, wobbly gait, few faeces, urine stain, ocular discharge, dehydration, rough coat, cool to the touch, hunched posture, protruding penus and dark material around the eyes, nose and mouth. Reductions in body weight and in weights of testes, liver and adrenals were observed at 25 000 and 50 000 ppm. The brain was examined retrospectively in the year 2000, and dose-dependent microscopic lesions (vacuolization) in the choroid plexus of the brain were observed at dietary concentrations of 5000 ppm (425 and 457 mg/kg bw per day for males and females respectively) and higher (Blair, 1997).

In a 28-day dose range-finding study, groups of three male and three female Fischer CDF (F344) Crl:Br rats received Proplant (containing 72.9% propamocarb-HCl) at a dose of 0, 20, 40, 100, 200, 500 or 1000 mg/per kg bw per day (expressed as active substance) by gavage. Animals were checked twice daily for clinical signs. Body weights and food consumption were measured on days –1, 8, 15, 22 and 28. All animals were necropsied and brain and exorbital lacrimal glands were examined microscopically.

Body weights of males at 1000 mg/kg bw per day and body-weight gain of males at 500 and 1000 mg/kg bw per day were decreased. Dose-dependent microscopic lesions (vacuolization) in the choroid plexus of the brain and lacrimal glands were observed at a dose of 200 mg/kg bw per day and higher (Blair, 2000).

Groups of 30 male and 30 female Wistar rats were fed diets containing propamocarb as Previcur N (propamocarb-HCl content, 66.5%) at 0, 200, 1000 or 5000 ppm (expressed as active ingredient), equal to propamocarb doses of 14, 72, and 362 mg/kg bw per day for males and 16, 79 and 396 mg/kg bw per day for females, for 13 weeks. Animals were checked twice daily for mortality and clinical signs. Body weight and food consumption were measured weekly. Water consumption was determined in weeks 1, 6 and 12. Ophthalomoscopy was performed pretest and at week 13. Haematology and clinical chemistry, including plasma and erythrocyte cholinesterase activity, was performed pretest and at weeks 7 and 13 on 10 animals of each sex per dose. Urine analysis was performed in weeks 7 and 13. At termination, all animals were macroscopically and histopathologically examined, organ weights were recorded and brain cholinesterase activity was measured. A statement of adherence to QA was provided.

No effects of treatment on mortality, clinical signs, ophthalmoscopy, clinical chemistry and haematology were observed. Small decreases in food efficiency (up to 8%), observed intermittently in males at 5000 ppm and in females at 1000 and 5000 ppm, and in body weight (6%) in females at 5000 ppm were considered to be not toxicologically relevant. Although statistically significant, the slight decrease ($\leq$ 6%) in absolute weight of liver and spleen and increase ($\leq$ 8%) in relative weight of brain and kidney in both sexes at the highest dose were not considered to be toxicologically relevant. Histopathological changes, observed in all groups including controls were considered spontaneous in origin. The activity of plasma and erythrocyte cholinesterase at weeks 7 and 13 and of terminal brain cholinesterase, determined in animals fasted for 24 h, was not inhibited. However, since it is known that blood and tissue concentrations of propamocarb peak shortly after oral administration and thereafter rapidly decline, and since effects of carbamates on cholinesterase activity are transient, the measurements in animals fasted for 24 h cannot be deemed sound.

The NOAEL for propamocarb-HCl was 5000 ppm (highest dose tested), equal to doses of propamocarb-HCl of 362 and 396 mg/kg bw per day for males and females respectively (Kojima & Enomoto 1982).

Groups of 10 male and 10 female Wistar rats received diets containing propamocarb as Previcur N (containing 64.3% propamocarb-HCl) at 0, 50, 500 or 5000 ppm for 5 weeks, equal to propamocarb-HCl doses of 0, 3, 34 and 421 mg/kg bw per day for males and 0, 3, 34 and 459 mg/kg bw per day for females. Variables examined were mortality, clinical signs, food and water consumption, body-weight changes, ophthalmoscopy, haematology, bone marrow, urine analysis, blood chemistry and blood coagulation. At termination the animals were necropsied, liver, kidney and heart weights were determined, and histopathological examinations of the liver, stomach, urinary bladder, kidneys, and heart were performed. A statement of adherence to QA was provided.

Small but statistically significant decreases in bone-marrow lymphocytes in male rats at 50 ppm and above and in female rats at 500 ppm and above were noted, together with a decrease in total serum cholesterol in male animals at 50 ppm and above, and an increase in serum sodium concentrations in males at 50 ppm and above and in females at 500 ppm and above. However, all these changes remained in the normal range for this strain of rats, and no organ damage was noted at any dose. The NOAEL for propamocarb-HCl was the highest dietary concentration of 5000 ppm, equal to 421 and 459 mg of propamocarb-HCl per kg bw per day (Staben & Schöbel, 1986).

In a 90-day dietary study, performed according to OECD guideline 408, groups of 10 male and 10 female Sprague Dawley rats received propamocarb-HCl liquid concentrate (containing 71.2% propamocarb-HCl) at a dose of 0, 7020, 14 040 or 28 080 ppm, equal to propamocarb-HCl doses of 318, 646 and 1363 mg/kg bw per day for males and 363, 716 and 1549 mg/kg bw per day for females. Statements of adherence to QA and GLP were provided.

No mortalities were observed. At the highest dose, a significant reduction in body weight (11% and 18% in males and females respectively) was observed. In these animals food consumption was also reduced (by 9% and 20% in males and females, respectively). At the intermediate dose, reductions in body weight (16%) and food consumption (9% less than controls) were seen in females.

Various small but statistically significant changes in absolute and relative organ weights were found in females at the intermediate and highest doses. However, since these changes were minimal and not associated with any histopathological findings, they are not considered to be toxicologically relevant. No treatment-related effects were observed at the lowest dose.

On the basis of the changes in body weight and food consumption in females at 14 040 ppm and higher, the NOAEL was 7020 ppm, equal to 363 mg/kg bw per day (Hubbard, 1998b).

In a 3-month study, performed according to OECD guideline 408, groups of 10 male and 10 female Wistar rats were fed diets containing Proplant (containing 75% propamocarb) at a concentration of 0, 375, 1500 or 6000 ppm, equal to propamocarb-HCl doses of 0, 28, 104 and 434 mg/kg bw per day for males and 0, 34, 130 and 540 mg/kg bw per day for females. Separate groups of controls and highest dose (10 animals of each sex per dose) were maintained for a further 28 days after treatment. Clinical signs were evaluated daily, body weight and food consumption were measured weekly, ophthalmoscopy was performed pretest and in week 13. The animals were tested in a functional observation battery (FOB) in week 13. At termination, blood was sampled for clinical chemistry, all animals were necropsied and organs were weighed. A wide range of organs and tissure was examined histologically. Statements of adherence to QA and GLP were provided.

No mortality was observed. At the highest dose, a reduction in body weight (females) and body-weight gain (both sexes) was observed from week 2 onwards. At this dose, microscopic lesions (vacuolization) in the choroid plexus of the brain and in the lacrimal glands were found and urinary sodium excretion was reduced in males. After cessation of treatment, recovery of these effects was observed, although the choroid plexus lesion was not completely reversible within the recovery period.

On the basis of the reductions in body weight and body-weight gain and the histopathological findings, the NOAEL was 1500 ppm, equal to propamocarb-HCl doses of 104 and 130 mg/kg bw per for males and females respectively (Schoenmakers, 2001a).

In a 52-week dietary study of toxicity, performed according to OECD guideline 452, groups of 20 male and 20 female Wistar rats received Proplant (containing 75.05% propamocarb-HCl) at a concentration of 0, 375, 1500 or 6000 ppm, equal to propamocarb doses of 0, 21, 84 and 356 mg/kg bw per day for males and 0, 29, 114 and 476 mg/kg bw per day for females. The animals were checked daily for mortality and clinical signs. Body weight was assessed weekly for the first 13 weeks and every second week thereafter. Food consumption was measured weekly. Ophthalmoscopy was performed pretest on all animals and on animals of the control and the group receiving the highest dose at week 25 and before termination. In weeks 50–51, 10 animals of each sex per dose were subjected to functional tests (hearing ability, reflexes, grip strength, motor activity). At weeks 13, 26 and 52, from 10 animals of each sex per dose that had been fasted overnight, blood was sampled for haematology and clinical chemistry and urine was collected for 16 h for analysis. At termination the animals were necropsied and selected organs were weighed. Brain, lacrimal gland, liver, kidneys and gross lesions from all animals

microscopically examined. Cholinesterase activity was measured in brain of four to five animals of each sex per dose. Statements of adherence to QA and GLP were provided.

No treatment-related effects on mortality, ophthalmoscopy, functional tests or food consumption were observed. Body weight and body-weight gain were slightly reduced in females at the highest dose. Alopecia was observed in females at the highest dose. Absolute and relative adrenal weight was increased in males at the highest dose. Relative brain weight was increased in the females at the highest dose. This was considered to be the result of the reduction in body weight and was not considered to be toxicologically relevant. Brain cholinesterase activity was not affected. An increased incidence of vacuolization in the choroid plexus and lacrimal gland ducts was observed in both sexes at the highest dose. Vacuolization of the choroid plexus was also increased in females at the intermediate dose. No treatment related neoplastic lesions were found.

On the basis of the increased vacuolization of the choroid plexus in females at the intermediate dose, the NOAEL was 375 ppm, equal to 29 mg/kg bw per day (Schoenmakers, 2002).

Dogs

In a range finding study, groups of one male and one female beagle dog were fed diets containing PrevicurN (propamocarb-HCl content, 68.4%) at a concentration of 0, 1000, 3000 or 10 000 ppm (equivalent to 0, 46, 119 and 386 mg of propamocarb-HCl per kg bw per day) for 28 days, followed by a 9-day recovery period. Animals were checked daily for mortality, clinical observations and food consumption. Body weight, and acetyl- and butyryl cholinesterase activity in plasma and erythrocytes were assessed before the start of the treatment and weekly thereafter. It is not clear how long after feeding the blood samples were taken. During the recovery period blood samples were taken at days 1, 6 and 9. At termination the animals were necropsied and cholinesterase activity in brain was assessed. A statement of adherence to QA was provided.

The only observed treatment-related effect was focal mucosal lesions in the stomach of the two dogs at 10 000 ppm. No effects on plasma, erythrocyte and brain cholinesterase activity were observed. Since the time spacing between feeding and blood sampling is not known the validity of the blood cholinesterase activity measurement cannot be established. Since brain cholinesterase activity was assessed after a 9-day recovery period, these data are irrelevant (Bathe et al., 1982).

Groups of four male and four female beagle dogs received diets containing propamocarb (purity unknown) at a concentration of 0, 50, 100, 500 or 1000 ppm for 90 days (at week 7 the highest dose was increased to 2000 ppm), equivalent to 0, 2, 4, 20 and 40/80 mg/kg bw per day. The study was performed according to USEPA guideline 82-1. Clinical signs were checked regularly. Body weights and food consumption were measured weekly. Haematology and urine analysis were performed pretest and at weeks 6 and 12. Biochemistry, including assessment of cholinesterase activity in plasma and erythrocytes was performed pretest, at day 4 and at 1, 2, 6 and 12 weeks. Liver and kidney function tests were performed in week 13. At termination the dogs were necropsied, organs were weighed and a full range of tissues and organs were histologically examined, and cholinesterase activity in brain was assessed. Statements of adherence to QA and GLP were provided.

Administration of test material at doses up to 1000/2000 ppm had no effect on mortality, clinical behaviour, body weight, food consumption, organ weights, haematology, clinical chemistry, cholinesterase activity, urine analysis, kidney or liver function, and no pathological changes were observed at the macroscopic or microscopic level. It is not mentioned how long after feeding blood and brain tissue samples for cholinesterase activity measurements were collected. Therefore the validity of the data on cholinesterease activity cannot be assessed.

In the absence of toxicologically relevant effects, the NOAEL was 1000/2000 ppm (the highest dose tested), equivalent to 40/80 mg/kg bw per day (Til, 1990).

In a 90-day study, performed according to OECD guideline 409, groups of four male and four female beagle dogs received diets containing Proplant (propamocarb content, 69.1%) at a dose of 0, 1000, 3000 or 10 000 ppm, equal to propamocarb-HCl doses of 0, 45, 131 and 433 mg/kg bw per day for males and 0, 51, 161 and 471 mg/kg bw per day for females. Clinical signs and food consumption were evaluated daily, body weight was measured weekly, ophthalmoscopy was performed pretest and in week 13. Blood and urine were sampled for clinical chemistry and urine analysis before treatment started and at weeks 6 and 13. All animals were necropsied and organs were weighed. A wide range of organs and tissues was examined histologically. Statements of adherence to QA and GLP were provided.

No mortality was observed. At the highest dose, food intake was reduced for the first 2–3 weeks, but was normal thereafter. At the end of the treatment period, in all animals in the group receiving the highest dose, degeneration of the eye fundus and hyporeflectibility was observed. At this dose, histological examination revealed vacuolar alteration of the trachea, oesophagus, fundus of the stomach, salivary glands, lacrimal glands, mandibular lymph nodes and bronchi/submucosal glands of the lungs. These findings were graded from slight to severe. In trachea, lungs and salivary glands of animals at 3000 ppm also vacuolar alterations were observed. Since these findings were graded as minimal, they are not considered to be of biological significance.

On the basis of the histological findings at 10 000 ppm, the NOAEL was 3000 ppm, equal to a dose of propamocarb-HCl of 131 mg/kg bw per day for males and 161 mg/kg bw per day for females (Schoenmakers, 2001b).

In a 1-year dietary study, performed according to OECD guideline 452, groups of four male and four female beagle dogs received Proplant (containing 69.1% propamocarb-HCl) at a concentration of 0, 1000, 2500 or 10 000 ppm, equal to a dose of propamocarb-HCl of 0, 39, 97 and 378 mg/kg bw per day for males and 0, 42, 116 and 405 mg/kg bw per day for females. Clinical signs were evaluated daily up to week 13 and weekly thereafter. Food consumption was measured daily. Body weight was measured weekly up to week 13 and biweekly thereafter. Ophthalmoscopy was performed pretest, in weeks 13, 26, 39 and at termination. Blood and urine were sampled for clinical chemistry and urine analysis before treatment started, at weeks 13, 26 and at termination. All animals were necropsied and organs were weighed. A wide range of organs and tissues was examined histologically. Statements of adherence to QA and GLP were provided.

No mortalities were observed. At the highest dose, females' food consumption was decreased and total protein concentrations in blood were reduced at week 13, 26 and at termination. In males at the highest dose, phospholipid concentrations were increased at week 13 and 26. At all doses, histological examination revealed an increase in the incidence and severity of vacuolar alterations in various organs and tissues of both sexes. At 1000 ppm, vacuolization was found in the adrenal cortex, duodenum (Brunner's glands), lungs (bronchial glands), stomach (pyloric glands) and tracheal glands. In addition, at 2500 ppm vacuolization, graded minimal to moderate, was observed in the epididymes, lacrimal glands, lymph nodes, oesophageal glands, salivary glands and uterine cervix. At the highest dose, vacuolization was also found in the kidney, testes and vagina. The severity of the findings was dose-dependent. Since these findings at the lowest dose were graded as minimal to slight, they are not considered to be of biological significance. In the eyes of all animals in the group receiving the highest dose and half of the males at the intermediate dose, degeneration of the eye fundus and hyporeflectibility was observed.

On the basis of histopathological changes observed at 2500 ppm and greater, the NOAEL was 1000 ppm, equal to doses of propamocarb-HCl of 39 and 42 mg/kg bw per day for males and females, respectively (Frieling, 2003).

In a 2-year feeding study, performed according to USEPA guideline 83-1, groups of six male and six female beagle dogs were fed diets containing Previcur N (propamocarb-HCl content 68%) at a concentration of 0, 1000, 3000 or 10 000 ppm (equal to doses of propamocarb-HCl of 0, 24, 71 and 243 mg/kg bw per day for males and 23, 73 and 228 mg/kg bw per day for females). One animal of each sex at the highest dose was maintained for a 29-week recovery period. Animals were checked daily for mortality and clinical signs. Food consumption was measured daily. Body weight was measured weekly. Ophthalmoscopy and a hearing test were performed pretest and at 3, 6, 9, 12, 18 and 24 months. In addition ophthalmoscopy was performed frequently in the two dogs during the recovery period. Haematology, clinical chemistry and urine analysis were performed pretest and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, 21 and 24 months. At termination all animals were examined macroscopically and histopathologically (including bone marrow) and organ weights were recorded. Statements of adherence to QA and GLP were provided.

Treatment with propamocarb had no effect on mortality, clinical behaviour, body weight, food consumption, haematology, blood chemistry, urine chemistry or hearing. At the highest dose, significant ocular effects (loss of colour and reflectability of the tapetum lucidum of the ocular fundus) were observed in both eyes of all animals after 40 weeks of treatment. In one male at the highest dose, subretinal haemorrhage and changes suggesting a focal choroiditis were found. Histopathological investigations of the ocular lesions showed that the effects were caused by degeneration of the cell-specific paraplasmatic inclusions (rodlets) and degenerative cytoplasmic changes in the tapetal cells. The tapetal changes were not reversible during the 29-week recovery period. Ultrastructural examinations indicated that the tissue adjacent to the tapetum, i.e. the retina and choroid, were not affected by the treatment.

Glomerulosclerosis, confined to the juxtamedullary area was found in three control dogs (minimal), one dog fed at 3000 ppm (minimal) and in four dogs given 10 000 ppm (minimal to moderate). Since this lesion was more severe at the highest dose, it may be treatment-related.

Slight to moderate chronic erosive gastritis and/or acute gastric mucosal erosions was observed in all groups, including the controls. The incidence of these lesions was significantly increased in treated male dogs compared with controls, although no dose–response relationship was observed. The severity of the lesions was not related to treatment. The toxicological relevance of this finding is not clear.

On the basis of the ocular effects and possible renal effects, the NOAEL was 3000 ppm Previcur N, equal to doses of propamocarb-HCl of 71 mg/kg bw per day for males and 73 mg/kg bw per day for females (Bathe, 1985).

(b) Dermal administration

Rats

Groups of five male and five female Sprague Dawley rats received dermal applications of propamocarb as Previcur N (propamocarb-HCl content 72%) at a dose of 100, 500 or 1000 mg/kg bw per day onto the clipped skin of the back under an occlusive wrapping (doses based on a range-finding study). Animals were dosed for 5 days per week during 3 weeks. Control animals were treated in the same manner but received no test article. Every day the test substance was removed 6 h after application. Observations were according to OECD 410. Statements of adherence to GLP and QA were provided.

No deaths occurred during the treatment period and no treatment-related systemic effects were observed in any animals. At 500 and 1000 mg/kg bw per day, scabbing at the treated skin sites was observed. Microscopy revealed ulcerative dermatitis comprising slight to severe acute dermatitis (acute inflammatory infiltration), slight to moderate epidermal hyperplasia, sloughing of the superficial tissues and eschar formation. In males these effects were dose-dependent with respect to incidence and severity.

The NOAEL for systemic toxicity was 1000 mg/kg bw per day of Previcur N, equal to a dose of propamocarb-HCl of 717 mg/kg bw per day. The NOAEL for local effects was 100 mg/kg per day of Previcur N, equal to propamocarb-HCl at 71.7 mg/kg bw per day (Healing, 1992).

In a study of dermal toxicity, which was performed according to OECD guideline 410, groups of five male and five female Wistar rats received dermal applications of propamocarb as Proplant (propamocarb, 69.1% w/w) at a dose of 0, 75, 300 or 1200 mg/kg bw per day (expressed as active substance) onto the clipped skin of the back under an occlusive wrapping (doses based on results of a 5-day range-finding study). The doses were applied for 6 h per day for 28 days. The animals were checked daily for clinical signs. Body weight and food consumption were measured weekly. The animals were tested in a FOB in week 4. At termination, blood was sampled for haematology and clinical chemistry. Animals were macroscopically examined, and selected organs were weighed. Histopathology was performed on a wide range of tissues. Statements of adherence to GLP and QA were provided.

There were three deaths (one at the lowest dose, two at the highest dose), which were not considered to be treatment-related. Treatment-related effects were only observed in females at the highest dose: a reduced body-weight gain, reduced cholesterol and albumin concentrations in the blood, reduced liver and thymus weight and vacuolization of the choroid plexus of the brain were observed. In addition the treated skin of the females at the highest dose revealed ulcerative inflammation, necrosis, erythema, wounds, scales and scabs.

On the basis of effects on body-weight gain, organ weights, cholesterol and albumin concentrations, and histological effects in the females at the highest dose, the NOAEL for propamocarb-HCl was 300 mg/kg bw per day. On the basis of effects on the treated skin in females, the NOAEL for local effects of propamocarb-HCl was 300 mg/kg bw per day (Van Otterdijk, 2002).

2.3 Long-term studies of toxicity and carcinogenicity

Mice

In a 104-week study of carcinogenicity, groups of 60 male and 60 female CD-1 mice received diets containing Previcur N (containing 70.2% propamocarb-HCl) at a concentration of 0, 20, 100 or 500 ppm (equal to doses of propamocarb-HCl of 0, 2.1, 9.7 and 52 mg/kg bw per day for males and 2.1, 10.8 and 54 mg/kg bw per day for females). Clinical signs were recorded daily for the first 4 weeks and weekly thereafter. Body weight and food consumption were measured weekly. At termination, all animals were necropsied. Histopathology was performed on all preserved tissue samples (including blood smears taken at 24 months, but not at 12 and 18 months) from animals in the control group and at the highest dose and on tissues from animals at the lowest and at the intermediate dose that showed macroscopic abnormalities indicative of neoplasia. Statements of adherence to QA and GLP were provided.

No treatment-related clinical signs of toxicity, mortalities, gross pathological findings, histopathological findings or effects on body weight, body-weight gain, food consumption and food efficiency, or tumour formation were reported.

The NOAEL was 500 ppm (the highest dose tested) equal to doses of propamocarb-HCl of 52 and 54 mg/kg bw per day for males and females, respectively (Hunter et al., 1983a).

In an 18-month study of carcinogenicity performed according to OECD guideline 451, groups of 50 male and 50 female CD-1 mice were fed diets containing Propamocarb-HCl Liquid Formulation (propamocarb-HCl content 71.2%) at a concentration of 0, 105, 840 or 6720 ppm, equal to doses of propamocarb-HCl of 0, 11, 84 and 690 mg/kg bw per day for males and 0, 12, 95 and 883 mg/kg bw per day for females. Two control groups of 50 animals of each sex per dose were used. Clinical signs and mortality were checked daily. Neurological perturbations,

impairment of dental growth and changes in the oral mucosa were assessed monthly. All animals were palpated for masses monthly for the first 6 months, and every 2 months thereafter. Body weight and food consumption values were recorded weekly. At 12 months and at termination, blood samples were taken for haematology. Ophthalmoscopic evaluations were performed pretest and in all survivors at 18 months. Selected organs were weighed, gross necropsies conducted and a complete list of tissues and organs examined microscopically. Statements of adherence to QA and GLP were provided.

There were no treatment-related clinical signs, mortalities, ocular effects or effects on food consumption, haematology, organ weight, gross pathology or histopathology. No effect of treatment on tumour incidence was found. Although body weights were decreased in females at the intermediate and highest doses, the reductions were small (about 5% and 7% respectively), and not considered toxicologically relevant. The NOAEL was 6720 ppm (highest dose tested), equal to doses of propamocarb-HCl of 690 and 883 mg/kg bw per day for males and females respectively (Hammerl, 1998).

In an 18-month study of carcinogenicity, performed according to OECD guideline 451, groups of 50 male and 50 female CD-1 mice were fed diets containing Proplant (propamocarb-HCl content, 75.05%) at a concentration of 0, 120, 840 or 6000 ppm (expressed as active ingredient), equal to doses of propamocarb of 0, 15, 106 and 790 mg/kg bw per day for males and 0, 19, 136 and 1014 mg/kg bw per day for females. Clinical signs and mortality were checked daily. All animals were palpated for masses weekly. Body weight and food consumption values were recorded weekly for the first 16 weeks and every 2 weeks thereafter. At 12 months and at termination, blood samples were taken for haematology. At termination selected organs were weighed and gross and microscopic examination was performed. Statements of adherence to QA and GLP were provided.

There was no treatment-related mortality. At the highest dose, small but statistically significant reductions in body weight (up to 8%) and body-weight gain (up to 17%) were observed in animals of both sexes. The incidence of emaciation was increased in females. No other treatment-related effects, including non-neoplastic and neoplastic changes were observed.

On the basis of reductions in body-weight gain, the NOAEL was 840 ppm, equal to doses of propamocarb of 106 and 136 mg/kg bw per day for males and females respectively (Schoenmakers, 2003).

Rats

In a long-term study of toxicity/carcinogenicity, groups of 70 male and 70 female Sprague-Dawley CD rats were given diets containing Previcur N (propamocarb-HCl content, 70.2%) at a concentration of 0, 40, 200 or 1000 ppm for 2 years. These concentrations are equal to doses of propamocarb-HCl of 0, 1.4, 7.3 or 37 mg/kg bw per day for males and 0, 1.8, 9.3 and 45 mg/kg bw per day for females (statement by the notifier). Animals were checked daily for clinical signs and mortality. Body weight and food consumption were measured weekly and water consumption over a 5 day period was recorded during weeks 6, 13 and 26. Ophthalmoscopy was performed on control and high dose animals before treatment and at weeks 13, 25, 52, 78 and 104. Haematology, clinical chemistry and urine analysis were performed for satellite groups of 10 animals of each sex from the control group and at the highest dose pretest and at weeks 12, 24, 50 and 78, and on 10 animals of each sex for all groups at week 103. During weeks 105 and 106, blood and urine samples for haematology, clinical chemistry and urine analysis were taken from all surviving animals. At week 52, five animals of each sex per dose were killed and macroscopically and microscopically examined and organ weights were recorded. At this time, another five animals of each sex per dose were placed on control diet for 4 weeks and subsequently underwent macroscopic examination and organ weight analysis. At termination gross pathological and microscopical examinations of tissues and organs were made. Selected organs were weighed. Statements of adherence to QA and GLP were provided.

No treatment-related effects were observed on body weight (< 4%), body-weight gain (< 5%), food consumption (< 7%), food conversion, water intake, ocular effects, organ weights, haematological, clinical biochemistry or urine analysis measurements. There were no treatment-related non-neoplastic histopathological findings. The JMPR in 1986 concluded that neoplastic lesions found in animals of the treatment groups were not treatment-related. In all groups infection with viral sialodacryo-adenitis, which was accompanied by slight reductions in food intake and body weight, occurred during weeks 5 and 41. Signs persisted up to 1 week. High mortality rates were observed in all groups (42–54% in males and 56–70% in females), including controls. The study is therefore of limited value (Hunter et al., 1983b).

In a long-term study of toxicity/carcinogenicity, performed according to USEPA guideline 83-5, groups of 70 male and 70 female Sprague Dawley Crl:CD(SD)BR rats were fed diets containing containing Propamocarb-HCL Liquid Concentrate (propamocarb-HCl content, 70.8–71.2%) at 0, 350, 2800 or 22 400 ppm, equal to does of propamocarb-HCl of 0, 10.4, 84 and 680 mg/kg bw per day for males and 0, 13.9, 112 and 868 mg/kg bw per day for females for 2 years. Clinical signs and mortality were checked daily. Detailed clinical examination, including palpation for masses, was performed weekly. Body weight was measured weekly for the first 14 weeks and every second week thereafter. Food consumption was measured weekly for the first 14 weeks and every 4 weeks thereafter. Water consumption of 20 animals of each sex per dose was recorded for periods of 4 days during each of weeks 9, 16, 32 and 48. Ophthalmoscopy was performed on animals in the control group and at the highest dose before treatment started and before the terminal kill. Haematology, clinical chemistry and urine analysis were performed on 10 animals of each sex per dose pretest and at 3, 6, 12, 18 and 24 months. From each group, 20 animals of each sex were used for the interim kill at 52 weeks. Animals of the interim kill and the terminal kill at 104 weeks were examined macroscopically and histopathologically. Selected organs were weighed. Statements of adherence to QA and GLP were provided.

No treatment-related effects on clinical signs, mortality, ophthalmology, haematology or clinical chemistry were observed. In males and females in the group receiving the highest dose, significant reductions in body weight (19% and 36% respectively), body-weight gain (25% and 51% respectively) and food (17% and 28% respectively) and water (13–21% and 21–32% respectively) consumption were observed. Statistically significant changes in absolute and relative organ weights were within historical control ranges or related to reduced terminal body weight, and not considered of toxicological relevance. Histopathology revealed vacuolization of the ependymal cells of the choroid plexus of the brain in all at the highest dose animals at both interim and terminal sacrifice times. No treatment-related effects on tumour incidences were found.

On the basis of effects on body weight, body-weight gain and the vacuolization of the ependymal cells of the choroid plexus of the brain at the high dose, the NOAEL was 2800 ppm, equal to doses of propamocarb-HCl of 84 and 112 mg/kg bw per day for males and females respectively (McFarlane & Buss, 1998).

In an addendum to the McFarlane & Buss (1998) study, the significance to humans of the vacuolization of the choroid plexus ependymal cells in rats, observed at 22 400 ppm was discussed.

It was concluded that this phenomenon was not caused by phospholipidosis, since staining of the choroid plexus for neutral fat (Sudan black) or lipoprotein (periodic Schiff) was negative in samples from males in the control group and at the highest dose and staining with toluidine blue did not indicate the presence of material within the ependymal cells. Therefore, the study authors considered the observed vacuolization to be the result of a species-specific localized effect on fluid homeostasis, i.e. accumulation of excess intracellular fluid. The study authors concluded that the vacuolization of the choroid plexus ependymal cells is not relevant for humans since it was recorded at very high doses in rats during long-term exposures, it was not recorded in studies in

the mouse or dog or in 90-day studies in rats, it was not associated with other histopathological findings in the brain or perturbations in behaviour, and it is highly unlikely that exposure of humans would occur at such high and prolonged levels (Jackson & Millar, 1999).

The Meeting noted that vacuolization of the choroid plexus was observed at low doses and in short-term studies. Vacuolization of the choroid plexus was observed in the rat in a 2-year study of oral toxicity (at 150 mg/kg bw per day, lowest dose tested; Blair, 2001b), in a 28-day range-finding study using gavage administration (at 200 mg/kg bw per day; Blair, 2000), a 90-day dietary study (at 434 mg/kg bw per day; Schoenmakers, 2001a), a 90-day gavage study (at 375 mg/kg bw per day; De Groot, 2002b), in a two-generation study of reproductive toxicity (at 200 mg/kg bw per day, (Thorsrud, 2002) and a 28-day study of dermal toxicity in rats (at 1200 mg/kg bw per day; Van Otterdijk, 2002). Although vacuolization in the choroid plexus was not observed in dogs, it cannot be excluded that propamocarb causes vacuolization in the ependymal cells in the human brain. Therefore, the Meeting considered that vacuolization of the choroid plexus is relevant to risk assessment for human health.

In a 2-year long-term study of toxicity/carcinogenicity, which was performed according to USEPA OPPTS guideline 870.4300, groups of 50 male and 50 female Fischer CDF(F-344) Crl:Br rats were fed diets containing Proplant (propamocarb content, 65.1%) at a concentration of 0, 2000, 5000 or 12 500 ppm, equal to doses of propamocarb (corrected for purity) of 0, 150, 368 and 989 mg/kg bw per day for males and 0, 155, 392 and 1022 mg/kg bw per day for females. Detailed clinical examination (including examinations for palpable masses) was performed weekly. Body weight and food consumption were recorded every two weeks for the first 13 weeks and every 4 weeks thereafter. Water consumption during one week was measured every 6 months. During weeks 27, 52, 78 and 104, blood and urine samples of 10 animals of each sex per dose were collected for haematology, clinical chemistry and urine analysis. Ophthalmology was performed pretest and at termination in 20 animals of each sex per dose. At termination all animals were macroscopically examined and organs were weighed. Microscopic examination was performed on all masses, on all organs and tissues collected from animals of the control and group receiving the highest dose and on animals that died or were euthanized. Statements of adherence to QA and GLP were provided.

There were no treatment-related mortalities. In the group receiving the highest dose, increases in clinical signs (urine stains, unkempt appearance, hunched posture, dark material around the eyes) were observed. No treatment-related effects on incidence or type of palpable masses were observed. Statistically significant reductions in body weight and food consumption were recorded in the groups receiving the intermediate and highest dose. The slight reductions observed in the group receiving the lowest dose were not considered to be toxicologically relevant. Statistically significant changes in haematology and clinical chemistry generally did not follow a consistent pattern and were not considered treatment-related. Reduction in creatinine concentrations in males at the highest dose may be indicative of muscle wasting, which may be secondary to the decreased body weight and food consumption. No treatment-related ocular lesions were observed. A dose-related and substantial increase in the incidence of vacuolization in the epithelial cells of the choroid plexus and the parenchyma of the lacrimal gland ducts was observed in both sexes of all treated groups. In the group receiving the highest dose, an increase in mononuclear cell leukaemias in females (highest dose, 19/50 = 38% versus control 11/50 = 22%) was observed. However, the incidence at the highest dose is within the range for historical controls (mean incidence for historical controls is 28%; upper range, 52%). Therefore, in this study propamocarb was not considered to be carcinogenic.

On the basis of the increased incidence of vacuolization in the epithelial cells of the choroid plexus and the parenchyma of the lacrimal gland ducts, the lowest-observed-adverse-effect level (LOAEL) was 2000 ppm, equal to doses of propamocarb of 150 and 155 mg/kg bw per day for males and females respectively. A NOAEL could not be identified (Blair, 2001b).

2.4 Reproductive toxicity

(a) Multigeneration study

Rats

Groups of 25 male and 25 female Wistar rats were given diets containing Previcur N (propamocarb-HCl content, 70.2%) at a concentration of 0, 40, 200 or 1000 ppm (equal to doses of propamocarb-HCl of 0, 2.1, 10 and 52 mg/kg bw per day for males and 0, 2.6, 13 and 65 mg/kg bw per day for females) for three generations. Two successive litters were reared from each female. The offspring from the first matings were reared to postnatal day 21 and then killed. The offspring (15 animals of each sex per dose) of the second litters (F_{1b} and F_{2b}) were used to produce the next generation. In addition, 10 animals of each sex per dose of the second litters were mated to be used for teratological examination. General condition and behaviour were routinely observed and individual body weights and food consumption were recorded throughout the study. The number of females rearing to 21 days postpartum, total litter loss and number of non-pregnant females and inseminated males was recorded from data collected during both the first and second matings. From the second matings, the number of total resorptions was recorded. The dams of the F_1 and F_2 generation that were selected for teratological examination were killed on day 19 of gestation. Preweaning, all litters were examined daily for mortality and abnormal pups, and physical development was assessed. Body weights were recorded at postnatal days 4, 12 and 21. F_{1b} and F_{2b} pups were examined for pupillary reflex and startle response on day 28 and learning ability in a water maze at day 60. At day 21 post partum, offspring in the F_{3b} generation litters was killed and subjected to macroscopic examination. From two males and two females of each F_{3b} litter, selected organs were weighed and organs and tissues of animals in the control and high-dose groups were subjected to microscopic examination. A statement of adherence to QA was provided.

No treatment-related effects on mortality and clinical signs were observed. In the parental generations, a slight reduction in food consumption was frequently observed during the pre-mating period in F_0, F_1 and F_2 male and/or females, primarily at the highest dose and the intermediate dose. In general, parental body weight, pregnancy rate, median pre-coital time, mating performance and duration of gestation were not affected by the treatment. Occasional decreases in body weight were not dose-dependent and not consistent over the generations, and are not considered to be of toxicological relevance. Over the three generations no treatment-related effect on sex ratio, pup weight on days 1 and 4 or litter size on days 1, 4, 12 and 21 were observed. In the F_0 and F_1 generations of the group receiving the intermediate dose, but not in the groups receiving the lowest or highest dose, increased incidences of total litter loss (first and second mating) were observed. In the F_{2b} litters of the group at the highest dose, an increase in early resorptions and preimplantation loss was observed. Decreased pup weights were observed on day 21 of the F_{1a} litters and on day 12 of the F_{1b} litters of the group at the highest dose. Preweaning physical development (hair growth, incisor eruption, opening of auditory canal and eye, pupillary reflex and startle response) were not affected. No teratological effects were observed in the offspring.

Since many of the effects observed in this three-generation study of reproductive toxicity were random, inconsistent and not dose-related, this study was considered as supplementary information (Allen et al., 1983).

In a two-generation study of reproductive toxicity, which was performed according to OECD 416, groups of 30 male and 30 female Sprague Dawley Crl:CD(SD)BR rats received diets containing Propamocarb-HCl Liquid Concentrate (propamocarb-HCl content, 71.1%) at a concentration of 0, 200, 1250 or 8000 ppm (equal to doses of propamocarb-HCl of 0, 9.2, 58 and 367 mg/kg bw per day for males and 0, 15, 90 and 569 mg/kg bw per day for females. Animals were observed twice daily for clinical signs of toxicity and mortality. Body weights were determined weekly. Body weights of females were measured on days 0, 4, 7, 10, 14 and 20 of

gestation and on days 1, 4, 7, 14 and 21 of lactation. Food consumption was measured weekly, but during gestation and lactation food consumption of females was measured daily. Reproductive parameters (e.g. fertility, mating, gestation duration, litter size, pup mortality) and endocrine functioning (estrus cycling, balanopreputial separation, vaginal opening, spermatogenic functioning and capacity) were recorded. At birth, all pups were sexed and examined for gross anomalies. Litters were examined daily for pup mortality and clinical signs. Pup weight was recorded at days 1, 4, 7, 14 and 21 after birth. At weaning on day 21, surplus pups were killed and necropsied, and reproductive and target organs from 10 animals of each sex in the control group and in the group at the highest dose were weighed and histologically examined. Statements of adherence to QA and GLP were provided.

Treatment-related effects were only observed at 8000 ppm and included the following: small but statistically significant reductions in body weight (up to 8%), body-weight gain (up to 13%) and food consumption (up to 15%) were observed in females of the F_0 generation and in males and females of the F_1 generation. Mean body weights of the F_1 and F_2 pups were similar to controls at birth but were reduced (by 6–8%) at days 14 and 21 of lactation. Absolute and relative spleen weights were reduced in pups of the F_1 generation, but not in F_0 and F_1 parental animals and pups of the F_2 generation. In female pups of the F_2 generation, absolute liver, kidney and adrenal weights were reduced. Since the relative weights were not affected, these effects may be related to lower body weights in these animals. Relative weights of liver, epididymis and pituitary glands in the male pups, and brain in the female pups of the F_2 generation were increased (up to 12 %). Similar effects were not observed in pups of the F_1 generation or in parental animals, and the toxicological relevance of the increased liver, epididymis and pituitary weight is not clear. No treatment-related effects on reproduction or on endocrine function were observed at any dose.

On the basis of the small but significant effect on body-weight gain, the NOAEL for parental toxicity was 1250 ppm, equal to 58 mg/kg bw per day for males and 90 mg/kg bw per day for females. On the basis of the reduced body-weight gain in the pups, the NOAEL for offspring toxicity was 1250 ppm, equal to 90 mg/kg bw per day (based on the intake of propamocarb in females). The NOAEL for reproductive effects was 8000 ppm, i.e. the highest dose tested, equal to 336 mg/kg bw per day for males and 569 mg/kg bw per day for females (Nemec, 1998).

In a study of reproductive toxicity, which was performed according to OECD guideline 416, groups of 28 male and 28 female Sprague Dawley rats were given Proplant (propamocarb content, 75.05%) at a dose of 0, 50, 200 or 1000 mg/kg bw per day by oral gavage for two generations. Treatment started 70 days before mating in the F_0 groups and at day 22 after birth in the F_1 generation, and was continued until the day before termination. Animals were checked daily for clinical signs and mortality. A detailed clinical examination was performed weekly on the animals of the F_0 generation. Body weights of the animals were measured weekly. After mating, body weights of females were measured on days 0, 7, 14 and 20 of gestation and during lactation on days 1, 4, 7, 14 and 21. Food consumption was measured weekly, except during cohabitation and lactation, when no food consumption data were collected. Other parameters measured were mating index and gestation duration, parturition, estrous cycle, sperm parameters (sperm count, concentration and motility). On day 4 after birth, litters were culled to four male and four female pups. At termination, all animals (parental and pups) were necropsied and selected organs were weighed. Histopathology was performed on the selected organs of parental animals. Offspring was monitored for clinical signs, viability and growth. F_1 pups selected to produce the next generation were examined for vaginal opening and preputial separation. Statements of adherence to QA and GLP were provided.

Mortality was increased at the highest dose (one and five males, and five and two females of the F_0 and F_1 generation, respectively) compared with the control group (only one female of the F_1 generation). In the group receiving the intermediate dose, five animals of the F_1 generation were found dead. Clinical signs in the group receiving the highest dose consisted of increased salivation before and after dosing, reddish material around the mouth and urine stains. Salivation

before and after dosing was also observed at the intermediate dose, albeit to a lesser extent. At several time-points, statistically significant changes in body weight and body-weight gain were observed in the treatment groups. At termination, in males at the intermediate and highest dose of the F_0 generation, slight (5%) reductions in body weight and food consumption were observed. No remarkable effects on the estrous cycle, fertility index, number of implantations, number of live pups or postimplantation loss were found. Sperm count and concentration and percentage of sperm with normal motility and morphology were reduced in F_0 and F_1 males at the highest dose. In males of the F_1 generation at the intermediate dose, a reduction in sperm count (17%, not statistical significant) and concentration (17%, statistically significant) was also found. Since the effects on sperm count and concentration in the F_1 generation at the intermediate dose were small and these sperm parameters were not affected in the F_0 generation at the intermediate dose, they are considered not to be toxicologically significant. Copulation index of the F_1 females in the groups receiving the intermediate and the highest dose was reduced and outside the historical control range of the investigating laboratory. F_1 females treated at the highest dose of the test material had a slight but statistically significant longer gestation than did the controls (22.3 versus 22 days). Survival of the F_1 and F_2 offspring at the highest dose was reduced, in particular during days 1 and 4 of lactation. Mean body weight at weaning was reduced (6–10%) in pups of the high dose group. In parental F_0 and F_1 animals at the intermediate and highest dose, specific vacuolar changes in the epithelial cells of the choroid plexus and epididymis were observed.

On the basis of the mortality, clinical signs and the specific vacuolar changes in the epithelial cells of the choroid plexus and epididymis, the NOAEL for parental animals was 50 mg/kg bw per day. The NOAEL for developmental toxicity was 200 mg/kg bw per day, on the basis of the decreased pup viability at the highest dose. The NOAEL for reproductive effects was 50 mg/kg bw per day on the basis of reduced copulation index at the intermediate dose (Thorsrud, 2002).

(b) Developmental toxicity

Rats

In a study of developmental toxicity, which was performed according to USEPA guideline 83-3, groups of 25 female Wistar-Han rats were given Previcur N (containing 68% propamocarb-HCl) at a dose of 0, 0.1, 0.3, 1.0 or 3.0 ml/kg bw per day, equal to doses of propamocarb-HCl of 0, 68, 204, 680 and 2040 mg/kg bw per day, orally by gavage during days 6 to 19 of gestation. Clinical signs and mortality were examined daily. Body weight, and body-weight gain were determined at days 0, 6, 15 and 20 of gestation. At termination on day 20 of gestation, the females were necropsied and ovaries and uterus were examined for number of corpora lutea, implantation sites, live and dead pups and early and late resorptions. Fetuses were weighed, sexed and examined for external, internal and skeletal abnormalities and anomalies. Statements of adherence to QA and GLP were provided.

At the highest dose, five out of twenty-five dams died, one because of an intubation error. Autopsy did not reveal any abnormalities. Severe signs of toxicity (blood stained snout, spastic gait, ruffled fur) were observed in dams at the highest dose and at termination body weight was reduced by 21%. Resorptions of all embryos occurred in five out of twenty surviving dams. Fetal body weight was decreased by 37%, and retarded ossification was observed. At 1.0 ml/kg bw per day, one dam died from unknown causes. No clinical signs of toxicity were observed. At 1.0 ml/kg bw per day, the number of dead fetuses was slightly increased and ossification of bone was retarded, although fetus weight was not affected. At doses of 0.3 ml/kg bw per day and higher, increased incidences (not dose-dependent) of fetuses with additional 14th ribs were found (in the groups at 0, 0.1, 0.3, 1.0 and 3.0 ml/kg bw per day, 19, 27, 42, 40 and 30% of the fetuses had an additional 14th rib, respectively). Since these increases in incidences were slight and not dose-dependent they were considered to be not toxicologically significant. No teratogenic effects were observed at any dose.

On the basis of the clinical signs of toxicity, reduced body weight and increased mortality the NOAEL for maternal toxicity was 1 ml/kg bw per day, equal to a dose of propamocarb-HCl of 680 mg/kg bw per day. On the basis of the slight increase in number of dead fetuses and the retarded ossification, the NOAEL for embryo/fetal toxicity was 0.3 ml/kg bw per day, equal to a dose of propamocarb-HCl of 204 mg/kg bw per day. In this study, propamocarb was not teratogenic (Poggel, 1990a).

In a study of developmental toxicity, which was performed according to OECD guideline 414, groups of 24 pregnant Wistar rats received diets containing Proplant (propamocarb-HCl content, 69.1%) at a concentration of 0, 375, 1500 or 6000 ppm, equal to an intake of propamocarb-HCl of 0, 31, 123 and 456 mg/kg bw per day, from day 6 to day 21 after mating. Animals were observed twice daily for the presence of clinical signs and mortality. Body weight and food consumption were recorded at the day of mating and every third day thereafter. At termination on day 21 all animals were necropsied. Ovaries and uterus were examined for number of corpora lutea, implantation sites, live and dead pups and early and late resorptions. Fetuses were weighed, sexed and examined for external, visceral and skeletal abnormalities and anomalies. Statements of adherence to QA and GLP were provided.

At 6000 ppm, body weight, body-weight gain and food consumption were reduced. At this dose fetal weight was reduced, both on litter and individual basis. Ossification was slightly retarded in the cranial bones, cervical and caudal vertebrae, humerus, fore- and hindlimb phalanges and metatarsals. The percentage of female fetuses was statistically significantly decreased, but remained within the range for historical controls. At 375 and 1500 ppm, no treatment-related adverse effects were observed.

On the basis of the reduced body weight, body-weight gain and food consumption the NOAEL for maternal toxicity was 1500 ppm, equal to a dose of propamocarb of 123 mg/kg bw per day. On the basis of the reduced body weight and slightly retarded ossification, the NOAEL for embryo/fetal toxicity was 1500 ppm, equal to a does of propamocarb of 123 mg/kg bw per day. In this study propamocarb was not teratogenic (Beekhuijzen, 2001).

Rabbits

In a study of developmental toxicity, which was performed according to USEPA guideline 83-3, groups of 18–22 female New Zealand White rabbits were given Previcur N (propamocarb-HCl content, 69.4%) at a dose of 0, 0.02, 0.06, 0.2, 0.4 and 0.8 ml/kg bw per day, equal to doses of propamocarb-HCl of 0, 13.9, 41.6, 139, 278 or 555 mg/kg bw per day, orally by gavage to during days 6 to 18 of gestation .

Clinical signs and mortality were examined daily. Body weight, and body-weight gain were determined at days 0, 6, 18 and 28 of gestation. At termination on day 28 the females were necropsied, and ovaries and uterus were examined for number of corpora lutea, implantation sites, live and dead pups and early and late resorptions. Fetuses were weighed, sexed and examined for external, internal and skeletal abnormalities and anomalies. Statements of adherence to QA and GLP were provided.

There was no treatment-related effect on mortality or clinical signs. Body-weight gain was significantly reduced during days 6–18 of gestation at the highest dose. The small reduction in body-weight gain at 0.4 ml/kg bw per day did not reach statistical significance. Recovery of body-weight gain occurred during the post-treatment period. An increased rate of abortion was found at 0.4 ml/kg bw per day, but not at 0.8 ml/kg bw per day. Postimplantation loss was increased at 0.4 ml and 0.8 ml (postimplantation loss in the groups at 0, 0.02, 0.06, 0.2, 0.4 and 0.8 ml/kg bw per day was 11.2%, 12.9%, 8.3%, 9.5%, 24.3% and 23.5%, respectively). The postimplantation loss at 0.4 ml was mainly attributable to one litter in which 11 of 12 fetuses were dead, and was considered to be incidental. The increased postimplantation loss at the highest dose was due to an increased incidence of resorptions and is considered to be treatment-related. Total litter loss, litter weight and pup weight were not affected. Macroscopic and histological examination revealed no

treatment-related teratogenicity in the pups. The incidence of 13th rib was increased in pups of the 0.8 ml/kg bw per day group (control: 32.5%; 0.8 ml: 48.1%).

On the basis of the reduced body-weight gain, the NOAEL for maternal toxicity was 0.4 ml/kg bw per day, equal to a dose of propamocarb-HCl of 278 mg/kg bw per day. On the basis of the increased postimplantation loss due to the increased incidence of resorptions, and increased incidence of 13th rib, the NOAEL for embryo/fetal toxicity was 0.4 ml/kg bw per day, equal to a propamocarb dose of 278 mg/kg bw per day. In this study, propamocarb was not teratogenic (Poggel, 1990b).

In a study of developmental toxicity, which was performed according to OECD guideline 414, groups of 29–32 pregnant New Zealand White rabbits were fed diets containing Proplant (propamocarb-HCl content, 69.1%) at a concentration of 0, 500, 2000 or 8000 ppm, equal to an intake of propamocarb-HCl of 0, 20, 76 or 269 mg/kg bw per day, from day 6 to 27 after mating. Animals were observed daily for clinical signs and mortality. Body weight and food consumption were recorded at the day of mating and every 3–5 days thereafter. At termination on day 28 all animals were necropsied. Ovaries and uterus were examined for number of corpora lutea, implantation sites, live and dead pups and early and late resorptions. Fetuses were weighed, sexed and examined for external, visceral and skeletal abnormalities and anomalies. Statements of adherence to QA and GLP were provided.

One animal in the control group and two animals at 500 ppm died. One animal at 2000 ppm was killed in extremis. At 8000 ppm, reductions in body weight, body-weight gain and food consumption were observed. No treatment-related fetal toxicity was observed.

On the basis of the reduced body weight, body-weight gain and food consumption, the NOAEL for maternal toxicity was 2000 ppm, equal to a dose of propamocarb of 76 mg/kg bw per day. The NOAEL for embryo/fetal toxicity was 8000 ppm, equal to a does of propamocarb-HCl of 269 mg/kg bw per day (highest dose tested). In this study, propamocarb was not teratogenic (Beekhuijzen, 2002).

2.5 Genotoxicity

The results of studies of genotoxicity with propamocarb are summarized in Table 2. The Meeting concluded that propamocarb is unlikely to be genotoxic.

2.6 Special studies

(a) *Neurotoxicity in vitro*

In a study in vitro, rat or beagle dog plasma was incubated at 37 °C for 10 min with propamocarb technical (purity, 98.5%) or Previcur N (propamocarb-HCl content, 67.5%) at doses of 0, 0.925, 9.25, 18.5, 37 or 74 mg/ml (expressed as propamocarb). Cholinesterase activity was assessed. A statement of adherence to QA was provided.

At a concentration of 37 and 74 mg/ml, propamocarb-HCl inhibited cholinesterase activity by 24% and 46% in rat plasma and by 33% and 60% in dog plasma respectively. Previcur N, at propamocarb-HCl concentrations of 37 and 74 mg/ml, inhibited cholinesterase activity by 22% and 40 % in rat plasma and by 29% and 53% in dog plasma respectively (Bhargava, 1981).

(b) Neurotoxicity in vivo after single doses

Rats

In a study of acute neurotoxicity, which was performed according to USEPA guidelines 81-8 and 82-7, groups of 10 male and 10 female Sprague Dawley rats were given Previcur N SL

(propamocarb-HCl content, 71.1%) as a single oral (gavage) dose at 0, 28, 281 or 2813 mg/kg bw, equal to doses of propamocarb-HCl of 0, 20, 200 and 2000 mg/kg bw, and were observed for 22–25 days. Clinical signs and mortality were assessed twice per day. Time of onset and recovery of clinical signs after dosing was recorded. A detailed physical examination, and measurements of

Table 2. Results of studies of genotoxicity with propamocarb

End-point	Test object	Concentration	Propamocarb-HCl content (%)	Result	Reference
In vitro					
Reverse mutation	*S. typhimurium.* Strains TA98, TA100, TA1535, TA1537 & TA1538, and *E. coli* WP2 *uvrA*	15–5000 µg/plate (±S9)	68.6	Negative	Jones & Fenner (1987)[a]
Reverse mutation	*S. typhimurium.* strains TA98, TA100, TA1535, TA1537 and TA1538. *E. coli* WP2*uvrA*	5–5000 µg/plate (±S9)	66.5	Negative	Kojima & Nakajima (1981) [b]
Reverse mutation	*S. typhimurium.* strains TA98, TA100, TA1535, TA1537 & TA1538.	50–5000 µg/plate (±S9)	72.2	Negative	Thompson (1997 [a]
Reverse mutation	*E. coli* WP2 *urvA*	33–2000 µg /plate (–S9) 3–5000 µg /plate (+S9)	69.1	Negative	Verspeek-Rip (2001a)[a]
Gene mutation	Mouse lymphoma L5178Y $Tk^{+/-}$ cells	3–2000 µg/ml –S9; 3–5000 µg/ml +S9	69.1	Negative	Verspeek-Rip (2001b)[a]
Gene mutation	Mouse lymphoma L5178Y $Tk^{+/-}$ cells	100–2500 µl/ml –S9; 125–4000 µl/ml +S9	71	Negative	Clare (2001)[a]
Chromosomal aberration	Human lymphocytes	110–1100 µl/ml –S9; 470–4700 µl/ml +S9	70	Negative	Allen et al. (1987)[a]
Chromosomal aberration	Human lymphocytes	518–4000 µl/ml –S9; 1000–5000 µg/ml +S9	69.1	Negative	Meerts (2001a)[a]
In vivo					
Micronucleus formation	Mouse bone marrow	1250, 2500 and 5000 mg/kg bw (gavage administration, twice, 24 h interval)	70.2	Negative	Hossack et al. (1980)[b]
Micronucleus formation	Mouse bone marrow	69, 138, 276 mg/kg bw (intraperitoneal injection)	69.1	Negative	Meerts (2001b)[a]
Dominant lethal mutation	Mouse	424, 755 and 1237 mg/kg bw per day for 8 weeks	69.2	Negative	Rushbrook & Jorgenson (1979)

Positive and negative (solvent) controls were provided in all studies.

[a] Statements of adherence to GLP and QA were provided.

[b] Statement of adherence to QA was provided.

body weight and food consumption were performed weekly. Neurobehavioural examinations (motor activity, FOB) were performed on days 1 (within 8 h after treatment), 8 and 15.

At termination, all animals were necropsied and histopathology was performed on nervous tissue and abnormal tissues observed at necropsy. Statements of adherence to QA and GLP were provided.

The only treatment-related effects, observed at the highest dose on the day of administration, were a reduced motor activity in females and an increased incidence of soiled coats in both sexes. No other treatment related effects were observed.

On the basis of the clinical signs and reduced motor activity, the NOAEL for Previcur N SL was 281 mg/kg bw, equal to a dose of propamocarb-HCl of 200 mg/kg bw (Ponnock, 1993).

In a study of acute neurotoxicity, which was performed according to OECD guideline 424, groups of 10 male and 10 female Wistar rats received Proplant (propamocarb content, 69.1%) at a dose of 0, 20, 200 or 2000 mg/kg bw per day (expressed as propamocarb-HCl) by gavage. The animals were tested for motor activity and in a FOB 1 week pretest and 1 h, 7 days and 14 days after dosing. Clinical signs were measured daily, body weights were measured pretest and on day 1 shortly after dosing and days 7 and 14. At termination, neuropathological examination was performed. Statements of adherence to QA and GLP were provided.

At 1 h after dosing, decreased motor activity (mean velocity, distance moved, number of movements) was observed in animals at the highest dose. At the intermediate dose, at 1 h after dosing, motor activity was reduced in males only. Although mean velocity was increased in females at the lowest dose, other related motor activity parameters were not affected and therefore this finding was considered to be incidental. At the highest dose females displayed hypothermia and decreased rearing activity. At day 7 no differences between groups were found. At day 14, the group receiving the lowest dose displayed an increased motor velocity. However, since related motor activity parameters were not significantly changed this finding was considered to be incidental. There was no evidence of treatment-related neuropathological effects at any dose.

On the basis of the decreased motor activity, observed 1 h after dosing in both males and females, the NOAEL was 200 mg/kg bw (De Groot, 2002a).

Dogs

One male and two female beagle dogs were given Previcur N (propamocarb-HCl content 67.5%) as a single oral dose (gavage) at 0.925 ml/kg bw, equal to propamocarb-HCl at 674 mg/kg bw . Clinical signs were recorded continuously. Acetylcholinesterase activity in plasma and erythrocytes was measured pretreatment and at 22–36 and 34–56 min after administration. Brain cholinesterase activity was measured in the "smell" brain of two dogs (one male, one female) that died. A statement of adherence to QA was provided.

In the male and in one female dog, chewing, shaking of the head, increased salivation, reddening of the skin around the snout, gait disturbances, tremors and convulsion followed by proneness (lateral position), dyspnoea, dark blue tongue and walking movements while prone were observed. The clinical signs started 15 min after dosing. Both animals were dead 51 min after dosing. The surviving female vomited and showed increased salivation. Treatment had no effect on plasma or erythrocyte acetylcholinesterase activity. Brain cholinesterase activity was reported to be in the normal range (Bhargava, 1981).

(c) Neurotoxicity after repeated exposures

Rats

Groups of 10 male and 10 female Sprague Dawley CD rats received Previcur N (propamocarb-HCl content, 70.2%) at an oral dose (gavage) of 0 or 3000 mg/kg bw per day, equal to doses of propamocarb-HCl of 0 or 2106 mg/kg bw per day, for 11 consecutive days. Animals

were checked daily for mortality and clinical signs. Body weight was recorded pretreatment, at day 7 and at termination. On day 7 of treatment, blood samples for cholinesterase measurements were taken predosing and at 0.5, 1, 2 and 3 h after dosing. At termination on day 11, rats were killed 30 min after the last dose and brains were removed immediately for analysis of brain cholinesterase activity.

During treatment, three males and eight females died. Salivation was observed in all animals of the treatment group, and occurred immediately after dosing and lasted for about 5 min. Body-weight gain was reduced in the treatment group. No inhibition of blood or brain acetylcholinesterase activity was observed (Hunter et al., 1978).

In a 3-month study of neurotoxicity, which was performed according to USEPA guideline 82-1, groups of 10 male and 10 female Sprague Dawley rats were given diets containing Previcur N SL (propamocarb-HCl content, 71.1%) at a concentration of 0, 281, 2813 or 28 129 ppm, equal to doses of propamocarb-HCl of 0, 14, 142 and 1403 mg/kg bw per day) for at least 90 days. Clinical signs and mortality were assessed twice daily. Time of onset and recovery of clinical signs after dosing was recorded. A detailed physical examination and body weight measurements were performed weekly. Food consumption was measured weekly to week 5 and twice weekly thereafter. Neurobehavioural examinations (motor activity, FOB) were performed pretest, and during weeks 5, 9 and 13. Plasma and erythrocyte cholinesterase activity was determined in five animals of each sex per dose during week 4 and at termination. At termination all animals were necropsied. Histopathology was performed on abnormal tissues observed during necropsy and on brain and peripheral nervous tissue of five animals of each sex per dose. Statements of adherence to QA and GLP were provided.

A decrease in body-weight gain (13–19%) was observed at the highest dose. No other treatment-related effects were observed.

On the basis of the reduced body-weight gain, the NOAEL was 2813 ppm of Previcur N SL, equal to a dose of propamocarb-HCl of 142 mg/kg bw per day (Ponnock & Bright, 1993).

In a 3-month study of neurotoxicity, which was performed according to OECD guideline 424, groups of 10 male and 10 female Wistar rats were given diets containing Proplant (propamocarb-HCl content, 69.1%) at a concentration of 0, 375, 1500 or 6000 ppm, equal to doses of propamocarb-HCl of 0, 25, 100 and 385 mg/kg bw per day for males and 0, 26, 104 and 406 mg/kg bw per day for females, respectively, for 101 to 104 days. Clinical signs were measured daily, body weight and food consumption were measured weekly. The animals were tested for motor activity and in a FOB pretest and in weeks 1, 4, 8 and 13 after the start of the treatment. At termination neuropathological examination was performed. Statements of adherence to QA and GLP were provided.

No treatment-related mortality or clinical signs were observed. Body weight and food consumption were reduced in females at the highest dose. No toxicologically relevant effects in the FOB or on motor activity were observed. Neuropathology revealed intra-epithelial vacuolization of the choroid plexus in the lateral, third and fourth ventricles in cerebrum and cerebellum of animals at the highest dose.

On the basis of the intraepithelial vacuolization of the choroid plexus, the NOAEL for Proplant was 1500 ppm, equal to a dose of propamocarb-HCl of 100 and 104 mg kg bw per day for males and females, respectively (De Groot, 2002b).

(d) Studies with impurities

Studies of acute toxicity and genotoxicity indicated no relevant differences between propamocarb and its impurities.

3. Observations in humans

In a statement regarding the medical surveillance of manufacturing plant personnel, it was reported that annual examination of the personnel had revealed no health effects of propamocarb. No dermal allergenic reactions had been detected (Kaleja, 1997).

No adverse health effects have been reported that are attributable to the synthesis, production and use of propamocarb or Previcur N (Davies, 1991).

A survey (performed by the notifier) on a number of national poison information centres revealed no reports on adverse effects of propamocarb (Anonymous, 1994).

In a data-bank search for clinical cases and poisoning incidents with propamocarb during 1978–2001, no reports on adverse effects on human health were found (Vafiadis, 2001).

Comments

Biochemical aspects

The kinetics of propamocarb have been studied in rats. After oral administration, propamocarb is rapidly and nearly completely absorbed with peak concentrations being reached within 1 h. Propamocarb is widely distributed, but was predominantly found in organs involved in elimination, i.e. liver and kidney. Elimination from tissues is rapid, with half lives ranging from 11 h to 26 h. Urine is the main route of excretion (about 75–91% of the administered dose within 24 h). Up to 6% of the administered dose is excreted in the faeces. Propamocarb is extensively metabolized. Unchanged propamocarb was found only in small quantities in the urine. Metabolism involves aliphatic oxidation of the propyl chain (to form hydroxypropamocarb) and *N*-oxidation and *N*-demethylation of the tertiary amine resulting in propamocarb *N*-oxide and mono demethyl propamocarb, respectively. No marked sex differences were observed in the absorption, distribution, excretion and metabolism of propamocarb.

Toxicological data

The acute toxicity of propamocarb is low. Oral LD_{50}s in the rat were ≥ 2000 mg/kg bw. The dermal LD_{50}s in the rat were > 2000 mg/kg bw. The inhalation LC_{50} in the rat was > 5.54 mg/l. In studies of acute oral toxicity, clinical signs of toxicity included hypokinesia, lethargy, hunched posture, body tremors, clonic convulsions, nasal haemorrhage, mouth haemorrhage, piloerection, staggering gait and ataxia within 24 h after dosing.

Propamocarb is not irritating to the eye or skin. It induced skin sensitization in a Magnusson & Kligman maximization test, but gave negative results in a Buehler test.

In many studies of short- and long-term toxicity in rats and dogs treated orally, histological examination revealed that propamocarb induces vacuolar alterations in cells. In the rat, propamocarb predominantly induces vacuolization of cells in the choroid plexus of the brain and in the lacrimal glands. In dogs, propamocarb-induced vacuolization was observed in a number of tissues (including the lacrimal glands), but not in the brain.

Short-term studies of oral toxicity were available for mice, rats and dogs. In two 3-month studies in mice, propamocarb did not induce any toxicologically relevant effects when tested at doses of up to 1952 mg/kg bw per day. Propamocarb was tested in two 4-week dose range-finding studies, and at doses of 3–1549 mg/kg bw per day in one 5-week, three 3-month and one 1-year dietary studies in rats. The main toxicological findings were reductions in body weight and vacuolization in the choroid plexus and the lacrimal glands. The lowest NOAEL for these effects, observed in a 1-year dietary study in rats, was 29 mg/kg bw per day, on the basis of vacuolization of the choroid plexus in females receiving a dose of 114 mg/kg bw per day. In a 3-month study

with a 28-day recovery period, partial recovery of the choroid plexus lesion was observed after cessation of treatment. The Meeting noted that for one 13-week study in rats the JMPR in 1984 had concluded that, "The study showed the no-effect level to be at least 200 ppm". The JMPR in 1986 had established an ADI of 0–0.1 mg/kg bw per day based, in part, on this study. The present Meeting concluded, however, that the observed effects in the treatment groups in this 13-week study were marginal and not toxicologically significant.

Propamocarb was tested in two 3-month, one 1-year and one 2-year dietary studies in the dog at doses ranging from 2 mg/kg bw per day to 471 mg/kg bw per day. The main toxicological findings were vacuolization in various organs. In a 3-month dietary study in dogs, the NOAEL was 131 mg/kg bw per day on the basis of vacuolar alterations in various organs. In a 1-year dietary study in dogs, the NOAEL was 39 mg/kg bw per day on the basis of vacuolization in various organs. In a 2-year study in dogs, the NOAEL was 71 mg/kg bw per day on the basis of an increase in the severity of glomerulosclerosis and loss of colour and reflectability of the tapetum lucidum of the ocular fundus. Since humans do not have a tapetum lucidum, the Meeting considered that the ocular effects in the dog were not relevant for humans.

The effects of dermal exposure to propamocarb were assessed in rats. In a 3-week study, no treatment-related systemic effects were observed at doses of up to 720 mg/kg bw per day (the highest dose tested). In a 4-week study in rats treated dermally, the NOAEL for systemic effects was 300 mg/kg bw per day on the basis of vacuolization of the choroid plexus of the brain and on reductions in body-weight gain, blood cholesterol and albumin concentrations and liver and thymus weight.

Long-term dietary studies have been performed in mice and rats. No carcinogenic effect of propamocarb was observed in any of these studies. In mice, no toxicologically relevant effects were observed in an 18-month study with doses of up to 883 mg/kg bw per day, and in a 2-year study with doses of up to 54 mg/kg bw per day. In another 18-month study in mice, the NOAEL was 106 mg/kg bw per day on the basis of reductions in body weight and body-weight gain.

In a 2-year study of toxicity and carcinogenicity in rats, minor decreases in food consumption (< 7%) and body weight (< 5%) were observed at a dose of 37 mg/kg bw per day (the highest dose tested). The present Meeting concluded that the small effects on food consumption and body weight were not toxicologically relevant. Since this study had several flaws, it was considered to be of limited value. In a second 2-year study of toxicity and carcinogenicity in rats, the NOAEL was 84 mg/kg bw per day on the basis of a decrease in body weight and body-weight gain and an increased incidence of vacuolization of the ependymal cells of the choroid plexus of the brain. In a third 2-year study of toxicity and carcinogenicity in rats, the LOAEL was 150 mg/kg bw per day (the lowest dose tested) on the basis of an increased incidence of vacuolization of the choroid plexus and the lacrimal gland ducts.

The Meeting concluded that propamocarb is not carcinogenic in rodents.

Propamocarb gave negative results in an adequate range of tests for genotoxicity in vitro and in vivo. The Meeting concluded that propamocarb is unlikely to be genotoxic.

In view of the lack of genotoxicity and the absence of carcinogenicity in mice and rats, the Meeting concluded that propamocarb is unlikely to pose a carcinogenic risk to humans.

In a two-generation dietary study of reproductive toxicity in rats, the NOAEL for parental toxicity was 1250 ppm (equal to 58 mg/kg bw per day for males) on the basis of reductions in body weight and body-weight gain. On the basis of a reduction in body-weight gain in the pups, the NOAEL for offspring toxicity was 1250 ppm (equal to 90 mg/kg bw per day based on the propamocarb intake in females). The NOAEL for reproductive effects was 8000 ppm (the highest dose tested, equal to 336 mg/kg bw per day). In a two-generation study of reproductive toxicity in rats treated by gavage, the NOAEL for parental toxicity was 50 mg/kg bw per day on the basis of clinical signs of toxicity and vacuolar changes in the epithelial cells of the choroid plexus and epididymis. The NOAEL for offspring toxicity was 200 mg/kg bw per day on the basis of decreased pup viability. The NOAEL for reproductive effects was 50 mg/kg bw per day on the basis of a reduced copulation index in females.

The effect of propamocarb on prenatal development was investigated in rats and rabbits. In none of the studies was propamocarb teratogenic. In a study in rats treated by gavage, the NOAEL for maternal toxicity was 680 mg/kg bw per day on the basis of clinical signs of toxicity, reduced body weight and increased mortality. The NOAEL for embryo- and fetotoxicity in this study was 204 mg/kg bw per day on the basis of a slightly increased incidence of number of dead fetuses and a delayed ossification. In a dietary study of developmental toxicity in rats, the NOAEL for maternal toxicity was 123 mg/kg bw per day on the basis of reduced body weight, body-weight gain and food consumption. The NOAEL for embryo- and fetotoxicity was also 123 mg/kg bw per day on the basis of reduced fetal weight and slightly delayed ossification of the cranial bones, cervical and caudal vertebrae, humerus, fore- and hind limb phalanges and metatarsals. The overall NOAEL for developmental toxicity in rats was 204 mg/kg bw per day. In a study in rabbits treated by gavage, the NOAEL for maternal toxicity was 278 mg/kg bw per day, on the basis of reduced body-weight gain. The NOAEL for embryo- and fetotoxicity was 278 mg/kg bw per day on the basis of increased postimplantation loss and increased incidence of a 13th rib. In a dietary study of developmental toxicity in rabbits, the NOAEL for maternal toxicity was 76 mg/kg bw per day on the basis of reduced body weight, body-weight gain and food consumption. The NOAEL for embryo- and fetotoxicity in this study was 269 mg/kg bw per day, the highest dose tested).

Studies of acute toxicity and short-term studies of oral toxicity in rats and dogs revealed no effect of propamocarb on cholinesterase activity in blood, plasma or brain, although when tested in vitro an inhibition of cholinesterase activity in rat and dog plasma was observed. In a single-exposure study of neurotoxicity, in which rats received propamocarb by gavage, the NOAEL was 200 mg/kg bw on the basis of reduced motor activity in females and increased incidence of soiled coats in both sexes. In a second single-dose study in rats treated by gavage, the NOAEL was 200 mg/kg bw per day on the basis of decreased activity 1 h after dosing in both sexes. In this study there was no evidence of treatment-related neuropathological effects 14 days after treatment with propamocarb at doses of up to 2000 mg/kg bw. In a 3-month dietary study of neurotoxicity in rats, the NOAEL was 142 mg/kg bw per day on the basis of a reduction in body-weight gain. In a study of neurotoxicity, in which rats received diets containing propamocarb for 101–104 days, the NOAEL was 100 mg/kg bw per day on the basis of intraepithelial vacuolization of the choroid plexus in both sexes and a reduction in body weight and food consumption in females.

In medical surveillance of manufacturing plant personnel and surveys of data banks of clinical cases and poisoning, no reports on adverse effects on human health were found.

The Meeting concluded that the existing database on propamocarb was adequate to characterize the potential hazards to fetuses, infants and children.

Toxicological evaluation

The Meeting established an ADI of 0–0.4 mg/kg bw based on a NOAEL of 39 mg/kg bw per day, on the basis of vacuolization observed in a range of organs in a 52-week study in dogs, and using a safety factor of 100.

The Meeting established an ARfD of 2 mg/kg bw based on a NOAEL of 200 mg/kg bw, on the basis of a decreased in activity in rats 1 h after dosing and using a safety factor of 100. This ARfD is adequately protective for effects observed in studies of developmental toxicity.

Levels relevant for risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	18-month study of toxicity[a]	Toxicity	840 ppm, equal to 106 mg/kg bw per day	6000 ppm, equal to 790 mg/kg bw per day
Rat	52-week study of toxicity[a]	Toxicity	375 ppm, equal to 29 mg/kg bw per day	1500 ppm, equal to 114 mg/kg bw per day

	2-year study of toxicity and carcinogenicity [a]	Toxicity	2800 ppm, equal to 84 mg/kg bw per day	22400 ppm, equal to 680 mg/kg bw per day
		Carcinogenicity	22400 ppm, equal to 680 mg/kg bw per day[c]	—
	Developmental toxicity [b]	Maternal toxicity	680 mg/kg bw per day	2040 mg/kg bw per day
		Fetotoxicity	204 mg/kg bw per day	680 mg/kg bw per day
	Acute neurotoxicity [b]	Neurotoxicity	200 mg/kg bw	2000 mg/kg bw
	101–104-day study of neurotoxicity [a]	Neurotoxicity	1500 ppm, equal to 100 mg/kg bw per day	6000 ppm, equal to 385 mg/kg bw per day
Dog	1-year study of toxicity [a]	Toxicity	1000 ppm, equal to 39 mg/kg bw per day	2500 ppm, equal to 97 mg/kg bw per day

[a] Dietary administration

[b] Gavage administration

[c] Highest dose tested

[d] Lowest dose tested

Estimate of acceptable daily intake for humans

0–0.4 mg/kg bw

Estimate of acute reference dose

2 mg/kg bw

Information that would be useful for the continued evaluation of the compound

Results from epidemiological, occupational health and other such observational studies of human exposures

Critical end-points for setting guidance values for exposure to propamocarb

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of absorption	Rapid and extensive (rats)
Distribution	Highest levels in liver, kidney, adrenals, spleen (rats)
Potential for accumulation	Low
Rate and extent of excretion	Rapid (75–91% in urine within 24 h in rats)
Metabolism in animals	Major metabolites: carbonyl propamocarb, hydroxy propamocarb, propamocarb-*N*-oxide, mono-*N*-demethyl propamocarb (rats)
Toxicologically significant compounds (animals, plants and environment)	Propamocarb
Acute toxicity	
Rat LD_{50} oral	≥ 2000 mg/kg bw
Mouse rat LD_{50} dermal	> 2000 mg/kg bw
Rat LC_{50} inhalation	> 5.5 mg/l air
Rabbit, skin irritation	Not an irritant
Rabbit, eye irritation	Not an irritant

Skin sensitization (test method used)	Sensitizing in guinea-pigs (Magnusson & Kligman) Not sensitizing in guinea-pigs (Buehler)
Short-term studies of toxicity	
Target/critical effect	Vacuolar changes in various tissues, reduction of body weight (rat, dog)
Lowest relevant oral NOAEL	1000 ppm, equal to 39 mg/kg bw per day (dogs)
Lowest relevant dermal NOAEL	300 mg/kg bw per day (rats)
Lowest relevant inhalatory NOAEL	No data
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Vacuolar changes in choroid plexus and lacrimal glands, reduction of body weight (rats)
Lowest relevant NOAEL	2800 ppm, equal to 84 mg/kg bw per day (rats)
Carcinogenicity	Not carcinogenic (mice, rats)
Genotoxicity	
	Not genotoxic in vitro or in vivo
Reproductive toxicity	
Reproduction target/critical effect	Reduced copulation index in females (rats)
Lowest relevant reproductive NOAEL	50 mg/kg bw per day (rats)
Developmental target	Reduced body weight and delayed ossification (rats); increased postimplantation loss (rabbits)
Lowest relevant developmental NOAEL	204 mg/kg bw per day (rats)
Neurotoxicity/delayed neurotoxicity	
Neurotoxicity	Decreased activity 1 h after a single dose administered by gavage (rats) Vacuolization of the choroid plexus in the brain after repeated dosing (rats)
Lowest relevant oral NOAEL	200 mg/kg bw (single dose by gavage) 52 mg/kg bw per day (repeated dietary dosing)
Other toxicological studies	
	No data
Medical data	
	No adverse effects reported in humans

Summary

	Value	Study	Safety factor
ADI	0–0.4 mg/kg bw	Dog, 1-year study of toxicity	100
ARfD	2 mg/kg bw	Rat, acute neurotoxicity	100

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