The EASE estimation (app. 5) of inhalation exposure during production and further processing of PCOC assuming use pattern is closed system and the pattern of control is full containment resulted in exposures of 0 to 0.1 ppm corresponding to 0 to 0.6 mg/m^3. This range is much lower than monitored data.

While some degree of dermal exposure may also occur, the EASE model predicts this as being of no consequence when compared with the inhalation route (app. 5). Direct contact with the skin would only happen in the case of accidents, where it could result in systemic toxicity as well as severe burns.

In conclusion the known corrosive nature of PCOC together with its use in the molten form ensures that routine transfer and equipment cleaning amd maintenance operations are performed with strict adherence to PPE requirements, resulting in minimal exposure to workers via both dermal and inhalation routes.

Application[2]: In certain occupational settings such as municipal gardening, worst case exposures may be higher. Using a standard model for plan protection product use (Lundeher, 1992) which also incorporates exposure during mixing and loading, a geometric mean exposure of 0.047 mg/kg/day is calculated for hand-held (knapsack) spraying of 1 ha assuming application of 2 kg/ha MCPA with a 1% content of PCOC and 100 % absorption. The 90th percentile exposure using the same inputs results in a total of 0.35 mg/kg/day.

4.1.1.3 Consumer exposure

PCOC is not found in any ordinary consumer products. It can occur as an impurity or breakdown product in herbicides used for controlling weeds in lawns of private gardens. One such product available in the vegetable section of a Danish super market contains MCPA in concentrations of 5.20 g/l in a one-liter plastic bottle provided with a hand pump for aerosol generation. As this form of dispensation can lead to the highest exposures, a realistic worst case for combined inhalation and dermal exposure of 10% is assumed. If PCOC is present as an impurity at 0.5%, and a further 0.5% is generated by exposure of the aerosol to sunlight, a total exposure to PCOC of 5.2 mg/event, or 0.07 mg/kg/event for a 70 kg person could result.

It is difficult to assess the frequency with which such consumer exposure might occur, directions for use on the particular product only state that it can be used during the entire growth period, but is most effective during periods of rapid growth in May, June, July and August (Source, "Toxan" - Labelling information, Distribution: Bayer Denmark A/S, Gammelager 1, 2605 Brøndby. In addition to MCPA, one liter of this product is also stated to contain 1.50 g Dichloprop-p and 0.32 g Dicamba as active ingredients). Assuming a really worst case of five times application per year the total yearly dose of PCOC would be 5 x 0.07 = 0.35 mg/kg/year (= 9.6x10^{-4} mg/kg/day).

2

During spraying, including mixing of pesticides, using sprayers on tractors the exposure is generally estimated to be around 0.00005% of the amount sprayed in a concentration of 15 g/ha using the best available technology. Using standard spraying equipment the exposure is 0.0002% of the amount sprayed (Lund & Kirknel, 1995).

Using a standard model for plant protection product use (Lundeher, 1992) which also incorporates exposure during mixing and loading, and assuming 2 kg MCPA per ha, with a 1% content of PCOC, a geometric mean exposure of 0.02 mg/kg body weight/day is derived, or for the 90th percentile, 0.28 mg/kg body weight/day for 20 ha of downward vehicle-mounted spraying.

4.1.1.4 Indirect exposure via the environment

Exposure of the environment can take place during the production of PCOC itself, as well as from the production and use of phenoxy herbicides.

At the production site the potential exposure would be through waste water and air effluent.

At sites of MCPA or other phenoxy herbicide applications, indirect exposure may occur, since PCOC is an impurity in the herbicide and has been identified as a degradation product of MCPA.

According to USES1.0 calculations involving local indirect exposure due to use of herbicides the following daily doses can be expected:

Intake air:	1.63×10^{-9} mg/kg/day
Intake drinking water:	8.95×10^{-8} mg/kg/day
Intake fish:	4.04×10^{-9} mg/kg/day
Intake stem of plant:	7.97×10^{-10} mg/kg/day
Intake root of plant:	3.38×10^{-12} mg/kg/day
Intake meat:	5.49×10^{-13} mg/kg/day
Intake milk:	5.47×10^{-13} mg/kg/day

Amounting to a total human dose of 9.60×10^{-8} mg PCOC/kg/day

The EUSES calculations (November 1997) for local indirect exposure resulting from production of PCOC are as follows:

	Ready degradability	Inherent biodegradability
Specific site*:	1.18×10^{-4} mg/kg/day	2.52×10^{-4} mg/kg/day
Formulation site**:	1.25×10^{-4} mg/kg/day	4.30×10^{-4} mg/kg/day

*: Specific site incl. production, processing and formulation. The values are based on average monitoring data on emissions from the two main manufacturers.

**: Formulation site is a generic site where it is assumed that 10 % of the total PCOC production is formulated (worst case).

We assume PCOC being readily biodegradable. However, knowing the substance may be a borderline case, the calculations for inherent biodegradability are included for comparison purposes only.

EUSES calculations (November 1997) for regional indirect exposure assuming ready or inherent (worst case) biodegradability. Again, inherent biodegradability has been included for comparison purposes only:

Daily human dose through:	Ready biodegradability	Inherent biodegradability
Intake air:	1.60×10^{-7} mg/kg/day	2.17×10^{-7} mg/kg/day
Intake drinking water:	4.49×10^{-6} mg/kg/day	8.05×10^{-6} mg/kg/day
Intake fish:	7.74×10^{-6} mg/kg/day	1.39×10^{-5} mg/kg/day
Intake from leaf crops:	2.44×10^{-7} mg/kg/day	3.31×10^{-7} mg/kg/day
Intake root of crops:	2.56×10^{-7} mg/kg/day	3.01×10^{-7} mg/kg/day

Intake meat:	$1.29x10^{-9}$ mg/kg/day	$2.25x10^{-7}$ mg/kg/day
Intake milk:	$7.60x10^{-10}$ mg/kg/day	$1.33x10^{-7}$ mg/kg/day
Regional total daily intake:	$1.29x10^{-5}$ mg/kg/day	$2.28x10^{-5}$ mg/kg/day

4.1.1.5 Combined exposure

Some parts of a population are exposed to PCOC both during work and during indirect exposure via the environment.

A person working at a production site for PCOC and/or phenoxy herbicides or a person spraying phenoxy herbicides on a field might apart from the occupational exposure also be exposed via the environment. However, the potential routes of exposure differs and as can be seen from 4.1.1.1., 4.1.1.2., and 4.1.1.3. the magnitude of the exposure varies greatly. In table 1 the calculated exposure data are given.

Table 1. Calculated exposure data excl. agricultural spraying[3]

Exposure	mg PCOC/kg/day
Occupational exposure during production	0.7
Spraying (municipal - hand spraying)	0.35
Consumer exposure	$9.5x10^{-4}$
Indirect regional exposure via the environment	$1.3x10^{-5}$
Local indirect exposure*	$1.2x10^{-4}$
Combined exposure, total	1.05 PCOC mg/kg/day

*: Local indirect exposure resulting from production, formulation or processing is estimated assuming ready biodegradability.

4.1.2 Effects assessment: hazard identification and dose (concentration) - response (effect) assessment

All the PCOC studies below that were performed by Scantox, Denmark and Teknologisk Institute were conducted in accordance with the OECD guidelines for testing of chemicals and GLP. The identity of the substance was as described in chapter 1 i.e. 97.09% 4-chloro-2-methylphenol, 1.21 % 6-chloro-2-methylphenol, 0.92% 2-methylphenol, and 0.78% 2,4-dichloro-6-methylphenol. The study by the Institute of Toxicology in Denmark (Hansen, 1996) used a 97% pure Aldrich PCOC batch no. C5.520-8. The study by Hattula *et al.* (1979) used 100% pure PCOC.

4.1.2.1 Toxico-kinetics, metabolism and distribution

Very little is known about the toxico-kinetics, metabolism, distribution, and excretion of PCOC in humans and experimental animals. However, from the acute toxicity studies it can be inferred that PCOC can be taken up in the body through the gastro-intestinal tract, the skin, and via inhalation. There is no information on the metabolism and excretion of PCOC.

[3] Table 1a. Calculated exposure data for agricultural spraying for comparison purposes only.

Exposure	mg PCOC/kg/day
Spraying (agricultural)	0.28

The concentrations of PCOC in liver, kidney, spleen, and muscle was studied in an acute and a repeat dose study (Hattula *et al.*, 1979). After 28 days of dosing by gavage with 100, 250, or 500 mg PCOC/kg, PCOC was found in the highest concentration 2.81 mg/kg in the spleen, and in the lowest concentration 0.27 mg/kg in muscle tissue in the high dose group. In the low dose group only traces of PCOC were found.

PCOC was found in concentrations of 47-31 µg/g in the liver of rats receiving 2-3 g/l MCPA in the drinking water for three months (Hattula *et al.*, 1977). A recent rat metabolism study with MCPA performed at Hazleton Lab. showed that PCOC was not a metabolite. It is therefore possible that the PCOC in the Hattula - study was a contaminant of MCPA (Jahanshahi J., 1995).

Acute toxicity

Animal data: Acute oral toxicity
In a guideline (401) study using five male and five female rats per group and dosing by gavage with the doses 1728, 2488, 3583 and 5160 mg/kg with oleum arachidis as vehicle, an LD_{50} of 3195 mg PCOC/kg (range 2698 - 3834 mg/kg) was found.

In the 5160 mg/kg group all animals died within one hour after dosing, in the 3583 mg/kg group 5 deaths occurred up to 6 hours after dosing, in the 2488 mg/kg group three deaths occurred within one day after dosing, and in the 1728 mg/kg group no deaths occurred. Symptoms observed just after dosing at all dose levels were paresis and depressions. On the second day, ruffled fur, which lasted to day five in the 3583 mg/kg group, was seen. Animals that died during the observation period showed bleeding in the mucous membrane of the stomach at autopsy. Animals sacrificed after the 14 days observation period showed no dose related macroscopic changes. However, two of the animals from the 2488 mg/kg group, sacrificed after the 14 days observation period, showed infiltrations between the oesophagus area of the ventricle and the diaphragm. In one animal from the high dose group, infiltrations between the oesophagus area of the ventricle and the liver were seen (Scantox, 1982b).

Groups of ten male Wistar rats, 2-3 months of age, were given 1000 , 1100, or 1200 mg PCOC/kg with the substance dissolved in olive oil. The animals were all killed 24 hours after dosing. A LD_{50} of 1190 mg/kg was derived (Hattula *et al.*, 1979). At the histopathological examination the following observations were made: At 1000 and 1100 mg/kg inflammatory mononuclear infiltration was seen in many glomeruli in the kidney. Inflammatory infiltrations were also seen in other parts of the kidney mostly around distal tubules. At 1200 mg/kg also histopathological alterations in the liver and spleen were seen. In the liver numerous pycnotic nuclei and hydropic degeneration of cytoplasm were observed. In the spleen the reaction centres were unusually large (Hattula *et al.*, 1979).

Further studies on the acute oral toxicity of PCOC to rats include BASF (1978) and Hazleton (1977). These test reports have not been available, but their results (see table 1) are in accordance with the results of the only guideline study available (Scantox, 1982b). It can be concluded that PCOC not only shows corrosive properties but also properties resulting in systemic effects i.e. effects on liver and kidney.

In rats the oral LD_{50} of PCOC is above 2.000 mg/kg in the most reliable study.

In mice, Schrötter *et al.* (1977) report the oral LD_{50} of PCOC as being 1330 mg/kg, but few experimental details are provided.

In range finding studies of PCOC in aqueous gum tragacanth emulsion, mice died consistently at lower doses (4/4 at 1200 mg/kg and 3/4 at 576 mg/kg) suggesting that the vehicle may play an important role in determining absorption following oral administration (Huntingdon, 1997).

Animal data: acute inhalation toxicity

Groups of five male and five female rats were exposed to an aerosol containing 0, 5.79, 8.33, 9.11, or 10% PCOC in 50% alcohol for 4 hours following OECD Guideline 403. All deaths during the study occurred during exposure or within the first hour after exposure. The deaths were distributed as follows between the groups: control 0 deaths, 5.79% 0 deaths, 8.33% two deaths, 9.11% four deaths, 10% 7 deaths. The LC_{50} was calculated as 900 mg/m^3 (0.9 mg/l range 0.83 - 1.08 mg/l) (Scantox, 1983a). The alcohol aerosol was used as it was not possible to generate a dust aerosol, as the test substance clumped. The LC_{50}-value is based on the nominal concentration in the experiment. The symptoms observed during and after exposure were respiration difficulties, depressions, ruffled fur and bleeding from the nose. These symptoms occurred in a dose related manner. Petechiae of the lungs were also observed.
At macroscopic examination of the animals that died up to the first hour after dosing bleeding of the lungs and a thin, mucous, yellowish content of the small intestine were found.

Another study was performed by Hazleton Lab in 1977 is cited from BUA (1994): The original report is not available and the study was carried out before guidelines were in general use. By inhalation of 2000 - 30.000 mg PCOC/m^3 (average particle size of 0.6 µm) for 4 hours no deaths occurred but swelling red noses and lips were seen. In one animal blood was found in the urine.

Animals sacrificed immediately after the exposure period or after 14 days of observation period showed no alterations in the lung or essential organs.

Animal data: acute dermal toxicity

Groups of five male and five female rats were dermally dosed with 1667, 2000, 2400, or 2880 mg PCOC in oleum arachidis in a guideline study (402). A LD_{50} of 2240 mg/kg (range 2023 -2484) was calculated from the observed deaths (Scantox, 1982c).

In the 2880 mg/kg group 9 animals died within 6 hours after dosing, in the 2400 mg/kg group six animals died within one day after dosing, in the 2000 mg/kg group four animals died within one day after dosing, and in the 1667 mg/kg group no animals died. At necropsy bleeding of the lungs, a mucous, red-yellow content of the jejunum, enlarged kidneys and blood or blood coagulum in the bladder plus bleeding of the bladder wall were observed.

During the first 24 hours after treatment blood was observed in the urine of all rats. From the day after treatment erythema and oedema at the application sites were seen. Paresis occurred in nearly all animals 1 to 6 hours after treatment. Depressions occurred up to 2 days after treatment, and ruffled fur up to 3 days after treatment. In animals sacrificed on day 14 weak bleeding of the intestine (jejunum) was observed in five of the rats (dose levels not stated).

In table 1 the acute toxicity data found for PCOC are given without any comments on quality of the studies.

Table 1. Data on acute toxicity of PCOC

species	application	dose	effect	literature

rat	oral	3.195 mg/kg	LD_{50}	Scantox, 1982b
rat	oral	1.190 mg/kg	LD_{50}	Hattula et al, 1979
rat	oral	2.650 mg/kg	LD_{50}	Hazleton Lab, 1977
rat	oral	2.700 mg/kg	LD_{50}	BASF AG, 1978 *
mouse	oral	1.330 mg/kg	LD_{50}	Schrötter et al, 1977
rat	i.p.	794 mg/kg	LD_{50}	Hattula et al, 1979
mouse	i.p.	570 mg/kg	LD_{50}	BASF AG, 1978 *
rat	inhal, 4h.	900 mg/m^3	LC_{50}	Scantox, 1983a
rat	inhal, 4h.	>30.000 mg/m^3	LC_{50}	Hazelton Lab., 1977
rat	dermal	2.240 mg/kg	LD_{50}	Scantox, 1982c
rat	dermal	>5.000 mg/kg	LD_{50}	Hazleton Lab,1977*

*: unpublished results sited in a BUA report (BUA, 1994).

In relation to acute oral, dermal and inhalation acute toxicity the Scantox Reports (1982b,c, 1983a) are found to be most reliable. For the acute oral toxicity the Hazleton and BASF studies support the oral LD_{50} found by Scantox. Poor reporting of the Hattula study makes its interpretation difficult. No details are available which would allow further interpretation of the Hazleton inhalation study.

The overall conclusion for acute toxicity is:

$LD_{50\ oral,rat}$ = 2650 - 3195 mg/kg
$LC_{50\ inh,rat}$ = 0.9 mg/l (as an EtOH aerosol)
$LD_{50\ dermal,rat}$ = 2240 mg/kg

4.1.2.2 Irritation

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4.1.2.3 Corrosivity

Animal data: skin irritation

In a guideline (404) study 6 female rabbits were dermally exposed to 0.5 g PCOC in 0.1 ml oleum arachidis. A primarily irritation index of 8.0, the maximum value obtainable, was calculated. Immediately after removal of the test substance the skin was white as a sign of initial necrosis (Scantox, 1982d).

BUA (1994) reports a study of Hazleton labs (1977), where rabbits received 500 mg PCOC on the shaved back in a semi-occlusive bandage. It is not stated if a vehicle was applied, and what time of exposure was used. After 12 hours necroses were observed and after 24 hours pronounced erythema with light oedema was observed

BUA (1994) reported a study of BASF where occlusive exposure to 80% of PCOC in water was carried out (species used and amount applied not mentioned). It was concluded that PCOC was very corrosive. After only one minute of exposure necrosis was found. After 20 minutes the necrosis was very pronounced, and after 8 days it had not disappeared. On day 8 after application the skin was still scarred.

In the rabbits eye BUA (1994) citing BASF reports 50 mg PCOC in an 80% aqueous solution as strongly corrosive. The eye turned red and after 1 hour oedema and opacity of the cornea was found. After 8 days the clinical observations were the same and a staphyloma was found.

In conclusion, some of the studies concerning corrosive effects of PCOC are cited from secondary references, but together with the results of the irritation test (Scantox, 1982d), they indicate that PCOC, according to EU criteria, may be classified as corrosive with R35: causes severe burns, in agreement with classification by the manufacturers.

At least one human fatality attributed to PCOC poisoning has been reported following exposure of the face and neck to a momentary blast of PCOC and steam during a workplace accident. It was not possible to estimate the dose or concentration involved (Pers. comm., HSE, U.K. 1996).

4.1.2.4 Sensitization

In a Guinea Pig maximization test carried out according to OECD guidelines (Scantox, 1982e) PCOC caused no sensitization. 40 female albino Guinea Pigs were used in the study. As the provocation test with 30% solution of PCOC caused erythema, a further provocation test with 10% and 20% of PCOC applied on the left and right flank, respectively, was carried out a week later. No clear differences between the control group and the test group were found at this occasion. Some animals of both groups were reacting with erythema (score 1-2). The reactions in the two groups were of the same magnitude. Macroscopically none of the reactions appeared to be an allergic.

The report by BUA (1994) mentions another negative sensitization study. However, the study does not seem to have been reported properly.

4.1.2.5 Repeated dose toxicity

There are three available studies on repeated dose toxicity of PCOC.

In a guideline (407) study groups of five male and five female rats were given 0, 50, 200, or 800 mg PCOC/kg in oleum arachidis by gavage for 28 days (Scantox, 1982a). During the last three days of dosing three rats from the 800 mg/kg group showed salivation after dosing, and on the last day of dosing three rats from the group had ruffled fur. Body weight gain and feed consumption did not differ between groups. In blood parameters *the thromboplastin time and the number of leukocytes were statistically smaller in females from the 800 mg/kg group. In males from the same group the erythrocyte count was statistically significantly reduced. Serum alanine-aminotransferase (ALAT)* was statistically significantly increased *in males of the 800 mg/kg group, and marginally increased in females*. In females from the 800 mg/kg group relative and absolute liver weights were significantly increased.

No histopathological changes were seen in any organ at 800 mg/kg. The changes of ALAT and liver weights in the 800 mg/kg group indicated *mild toxicity to the liver*. It was concluded in the test report that 800 mg/kg is a LOAEL, and that *200 mg/kg is a NOAEL*.

Hattula *et al.* (1979) dosed groups of ten male Wistar rats with 0, 100, 250, or 500 mg PCOC/kg in olive oil for 28 days by injection (gavage). It is very difficult to interpret the results of this study, basically because of lack of tables and explanations to the few tables given. However, at 100 mg/kg all investigated organs were normal except for the small intestine, which had necrotic areas of the mucosa. The dose relationship of the other histopathological observations mentioned is obscure. It is stated that

blood analyses showed that leukocytes were decreased with larger doses. *At 500 mg/kg a clear-cut leucopenia was found.*

In a combined *repeated dose/reproduction screening test* carried out according *to OECD draft guideline 422* (Ernst Hansen, "4-Chloro-2-methylphenol," National Food Agency, 1996) groups of 10 male and 10 female rats per dose were given 0, 50, 200, or 600 mg PCOC/kg in soybean oil by gavage for two weeks prior to mating until day 20 of gestation i.e. dosing was for a total of 40-45 days.

Weight gain was slightly reduced, and water consumption increased in the highest dose groups. *Males in the 600 mg/kg group showed a decrease in haemoglobin concentration ($p<0.01$).* (A slight decrease in plasma creatine ($p<0.05$) in the middle dose group was considered to be without physiological significance.)

A dose-related decrease in the absolute and relative weight of the adrenals of female rats was seen ($p<0.05$ at 200mg/kg, $p<0.01$ at 600 mg/kg) but was unaccompanied by histopathological changes, and without obvious toxicological significance.
No effects were seen in other macroscopic and histological examinations of the organs. No behavioural changes were found by a functional observational battery, or in motor activity. It was concluded that the NOAEL was 200 mg/kg.

With regard to respiratory irritation and corrosivity after repeated dosing no data are available. However, due to the caustic properties of the substance it seems unlikely that an inhalation study would add any new information on the systemic toxicity. Further, it seems that the way the substance is handled and used in the existing productions do not lead to any respiratory problems. At both production sites health surveillance programmes including examination of the respiratory function have been undertaken for several years. According to the medical reports submitted by the producers no significant increase in any specific symptoms such as sore throats, coughs and changes of lung function and no significant group changes of lung function have been observed (A.H. Marks, 1997b; Nufarm, 1997b).

4.1.2.6 Mutagenicity

Genetic toxicity *in vitro*

According to Ames, et. al. 1975, and/or OECD guideline 471 four direct plate Ames tests (Räsänen *et al.*, 1977 ; Teknologisk Inst, 1982; Strobel & Grummt, 1987; BASF, 1988) and one pre-incubation Ames test (BASF, 1988) have been carried out to study the mutagenicity of PCOC in the dose range 1-500 µg/plate.

Ames direct plate test was performed with the *Salmonella typhimurium* strains TA1537, TA1535, TA100, and TA98 at 0, 1, 5, 10, 50, 100, and 500 µg/plate with and without metabolic activation. The identity of the substance was as described in chapter 1. There was clear general toxicity in all strains at 500 µg/plate, but none of the strains showed an increase in the number of revertants/plate (Teknologisk Institut, 1982).

Ames direct plate test was performed with the *Salmonella typhimurium* strains TA1537, TA1535, TA100, and TA98 at 0, 0.5, 5, 50, and 500 µg/plate with and without metabolic activation. None of the strains showed an increase in the number of revertants/plate (Räsänen *et al.* 1977).

Ames direct plate test was performed with the *Salmonella typhimurium* strains TA1537, TA1535, TA100, and TA98 at 0, 20, 100, 500, 2500, and 5000 µg/plate and at 0, 4, 20, 100, 500, and 1500

µg/plate with and without metabolic activation. There was clear general toxicity in all strains at and above 500 µg/plate, and none of the strains showed an increase in the number of revertants/plate (BASF, 1988).

An Ames direct plate test using the strains TA98, TA100, TA97 and TA104 at 10, 25, 50, 100, 250, 500, and 1000 µg/plate with and without metabolic activation showed a 4.4 fold dose related increase with TA97-S9 and a 5.4 fold dose related increase with TA97+S9. Only these results were significant. At the highest dose a toxic effect was found in all the strains (Strobel & Grummt, 1987). The report of these results in the literature leaves open some questions with regard to the interpretation of results. For this reason an additional test was performed.

In this new test, 97% PCOC (Aldrich lot no. 3302005) was dissolved in DMSO and tested according to the Salmonella/microsome standard plate assay in *S. typhimurium* strains TA-97 and TA-98 at doses of 500, 250, 100, 50, 25 and 10 ug/plate with and without S9-mix (at 2 and 4 mg S9 protein/plate). No mutagenic effect was seen with or without metabolic activation in either strain. The experiments were repeated again with the same results. (Binderup, "4-Chloro-2-methylphenol: Assessment of mutagenic potential," National Food Agency of Denmark, 1996:)

In the Ames test with pre-incubation (BASF, 1988) *Salmonella typhimurium* strains TA1535, TA100, TA1537, and TA98 was used with and without metabolic activation in concentrations of 0, 4, 20, 100, 500, and 1000 µg/plate and 0, 15, 30, 60, 125, and 250 µg/plate (two separated series). General toxicity occurred at dose levels of 125 µg/plate or higher. There was no increase in the number of revertants/plate.

Genetic toxicity *in vivo*

In a micronucleus assay performed according to the first version of OECD guideline 474 male and female mice were dosed by gavage with 1600 mg PCOC/kg in 10 ml of peanut oil, corresponding to the maximum tolerable dose. Bone marrow cells were harvested at 24, 48, and 72 hours post dosing. A significant ($p < 0.0007$) increase (4-6 times) in the frequency of micronuclei was observed in the dosed animals at all harvesting times (Scantox, 1982f). It was noted that there was no clear evidence of a time-course for these effects. The incidences of micronucleated cells in treated animals were not particularly high compared to published data for untreated mice, while the incidence in the control group was lower than what would usually be expected. It was not possible to re-examine concurrent control data to obtain information on background rates, as the records are no longer available.

A new mouse micronucleus assay was performed in 1997 according to current guidelines (EEC , 29 December 1992, Official Journal of the European Communities No. L358B: Methods for determination of toxicity, B12: Mutagenicity (Micronucleus test) p. 124), including the OECD guideline revision (OECD 1996) recommending use of aqueous suspending agents for poorly soluble substances. The test substance, 99.3% pure PCOC consisting of 50% of current production lots from each of the two U.K. producers was suspended in aqueous 0.5% gum tragacanth. A preliminary toxicity test indicated that in this vehicle, the maximum dose which did not induce excessive lethality was approximately 400 mg/kg. For the Micronucleus test, groups of 5 male and 5 female mice were dosed by gavage with 20 ml/kg suspensions of test substance corresponding to 100, 200 and 400 mg/kg body weight of PCOC, using the vehicle alone as the negative, and Mitomycin C as the positive control.

Severe lethargy was noted shortly after dosing at 400 mg/kg. One female in the high dose group died , and was replaced by another female from the concurrently-treated satellite group. No adverse clinical signs were observed for the positive or negative control groups during the duration of the test.

Bone marrow samples were examined (1000 erythrocytes per smear) after 24 hours and 48 hours and did not show any substantial increase in the incidence of micronucleated immature erythrocytes or decrease in the proportion of immature erythrocytes. It was concluded that PCOC did not show any evidence of causing chromosome damage or bone marrow cell toxicity in this test. The positive control caused highly significant (P<0.001) increases in the number of micronucleated immature erythrocytes at both 24 and 48 hours. Results for PCOC treated and control animals were within the expected range for unaffected mice based of published information and laboratory control data (Huntingdon, 1997).

While cytotoxic effects were not seen in the bone marrow, there is little to suggest that PCOC would not be absorbed, or would break down prior to reaching this site. Clear evidence of leukopenia seen in the two repeat-dose studies is highly suggestive bone marrow effects. *In vivo* mutagenicity studies of the meta isomer of chlorcresol (4-Chloro-3-methyl phenol, Cas. no. 59-50-7) showed a similar pattern, with no change in the observed PCE/NCE ratio and no clastogenic activity (mouse micronucleus test, oral, 200 and 400 mg/kg, 24 hours: mouse micronucleus test, single i.p. injection of 125 mg/kg - 10 % mortality - investigations at 24, 48 and 72 hours post dosing, stat. significant response in cyclophosphamide control) (BUA, 1993 - U.S. EPA 1997).

Conclusion on mutagenicity.

PCOC was negative in 3 Ames tests, equivocal in one, and negative in repeat tests of the equivocal strain. An oral mouse micronucleus performed in 1982 according to the first OECD guidelines was positive. A repeat of this test in 1997 using modern guideline recommendations and possibly a more suitable test vehicle was clearly negative. Using the best available data PCOC cannot be considered a mutagen.

4.1.2.7 Carcinogenicity

For 4-chloro-o-cresol (PCOC) no studies in humans or animals are available.

Human data on phenoxy herbicide production

A cohort study of workers employed in manufacturing of phenoxy herbicides, primarily MCPA, in Denmark before 1982 was carried out. The study seems to support the Swedish observation of an increased risk of soft tissue sarcomas following exposure to phenoxy herbicides. The purpose of the study was to shed further light on the potential carcinogenic effect indicated by a Swedish case control study of the 2,4-dichlorophenol and 4-chloro-o-cresol based phenoxy herbicides unlikely to be contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin.

Cancer cases were identified by linkage with the National Cancer Register. Special attention was given to soft tissue sarcomas and malignant lymphomas. Five cases of soft tissue sarcomas were observed among male employees in contrast to 1.84 expected cases, RR=2.72, CI95 =0.88-6.34 (Lynge, 1985).

An update of the above mentioned cohort study (Lynge, 1993) adds data for the period 1983-87. Based on small numbers the study adds to the evidence for a possible association between phenoxy herbicide exposure and risk of soft tissue sarcomas. There are, however, a number of possible confounders in these studies, and the overall cancer incidence of workers employed in manufacturing and packaging of phenoxy herbicides was the same as for the Danish population (66 observed v. 64.27 expected, SIR 1.0, 95% CI 0.8-1.3).