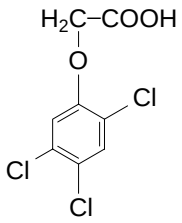
2,4,5-Trichlorophenoxyacetic acid H (2,4,5-T) including Salts and Esters

Classification/MAK value:	**10 mg/m^3 I** **Peak limitation category II,2** **Pregnancy risk group C**
MAK value dates from:	**1995**
Synonyms:	2,4,5-T
Chemical name (CAS):	2,4,5-trichlorophenoxyacetic acid
CAS number:	93-76-5
Structural formula:	
Molecular formula:	$C_8H_5Cl_3O_3$
Molecular weight:	255.48
Melting point:	156.6°C

2,4,5-Trichlorophenoxyacetic acid (2,4,5-T) compounds have been used as herbicides. Their use has been banned in Germany since 1988. Depending on the production process, 2,4,5-T formulations contained differing amounts of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and other polychlorinated dibenzodioxins. In 2,4,5-T samples from the 1950s and 1960s TCDD concentrations of over 1000 ppb were detected; in 1986 a threshold value of 5 ppb was set for TCDD.

When evaluating TCDD as an impurity in various chloro-organic compounds, the toxicity of the different components of the mixtures must be taken into consideration. For this reason the present documentation for 2,4,5-T was drawn up.

A paper on 2,4,5-T has appeared as part of the review of data for the toxicology of herbicides prepared by the toxicology group of the DFG Pesticides Commission (DFG 1982). These data are summarized here. Studies on the parameters important for the assessment of 2,4,5-T, reproductive toxicity, carcinogenicity and genotoxicity, and those published since appearance of the above report are described in more detail.

1 Toxic Effects and Modes of Action

2,4,5-T is readily absorbed both orally and dermally and is eliminated via the kidneys mainly unchanged. 2,4,5-Trichlorophenol was identified in small amounts as one of the metabolites. The target organs in the rat after several doses of 2,4,5-T are the kidneys and liver. A no observed effect level (NOEL) for 2,4,5-T of 3 mg/kg body weight was found for rats after both medium-term and long-term exposure. Medium-term studies yielded a NOEL for dogs of 2.4 mg/kg body weight. Except for a suspected weak clastogenic effect *in vitro*, neither genotoxic nor carcinogenic effects were found. Reduced foetal body weights were observed in mice after doses of 2,4,5-T of about 15 mg/kg body weight and more and there was an increase in the incidence of cleft palate from about 30 mg/kg body weight. In rats there was an increase in the number of resorptions from about 50 mg/kg body weight; an increase in cleft palate or teratogenic effects only occurred in isolated cases after doses of 100 mg/kg body weight.

There are no data available on the mechanisms of action of 2,4,5-T.

2 Toxicokinetics

2,4,5-T is absorbed readily by man and animals both orally and dermally. In analogy to 2,4-dichlorophenoxyacetic acid (2,4-D, this volume) it can be assumed that the acid is formed from the salts and esters both in the stomach and in the skin, and is then rapidly absorbed. In plasma 2,4,5-T is found mainly bound reversibly to plasma proteins (Fang and Lindstrom 1980, Gehring *et al*. 1973). Absorption into organs such as the kidneys (Hook *et al*. 1976, Koschier and Berndt 1977) and brain (Tyynelä *et al*. 1990) takes place via active transport mechanisms (Piper *et al*. 1973). 2,4,5-T binds more strongly to plasma proteins than does 2,4-D; this is why 2,4,5-T enters the brain to a lesser extent than does 2,4-D (Tyynelä *et al*. 1990). The half-time for elimination from the plasma after oral administration of 2,4,5-T doses of 5 mg/kg body weight was found to be 23.1 hours in man (Gehring *et al*. 1973) and 4.7 hours in the rat (Piper *et al*. 1973). After 5 days, more than 80 % had been eliminated in man and rats (Fang *et al*. 1973, Gehring *et al*. 1973, Piper *et al*. 1973). It was shown in rats that with increasing concentrations of 2,4,5-T the half-times increase (after 100 mg/kg body weight 19.4 hours; Piper *et al*. 1973). Dogs are more sensitive to the effects of 2,4,5-T; this is attributed to the fact that 2,4,5-T is eliminated more slowly by dogs and therefore remains in the body longer (half-life 77 hours) (Piper *et al*. 1973).

2,4,5-T is excreted mainly in unchanged form with the urine by man and rats (Fang *et al*. 1973, Grunow and Böhme 1974). Small amounts of glycine and taurine conjugates and 2,4,5-trichlorophenol were also detected (Grunow and Böhme 1974). The amount excreted with the faeces in rats is low and accounts for only 3.2 % of doses in the range of 5 mg/kg body weight. After higher doses and the consequent saturation of renal excretion, the amount excreted with the faeces increases (9.1 % after administration of 100 mg/kg body weight; Piper *et al*. 1973). In dogs, which have a lower renal excretion

capacity, more 2,4,5-T is excreted with the faeces (9 days after 5 mg/kg body weight 42 % in the urine and 20 % in the faeces; Piper *et al*. 1973).

3 Effects in Man

3.1 Absorption

For workers spraying 2,4,5-T herbicides from containers worn on the back, the average dermal absorption was determined as 0.08 to 1.85 mg/kg body weight. In contrast, only about 0.002 mg/kg body weight was absorbed by inhalation (DFG 1982).

3.2 Acute toxicity

Single oral doses of 5 mg/kg body weight produced no clinical effects in 5 volunteers. Doses of 3 to 4 g 2,4,5-T per person led, however, to clinical symptoms (DFG 1982).

3.3 Reproductive toxicity in man

There are no studies available on the influence of 2,4,5-T on male or female fertility.

The available studies deal exclusively with the possible effects on children whose fathers or mothers were exposed before the birth to 2,4,5-T and therefore also to TCDD (Table 1). The exposed fathers were herbicide sprayers or army personnel who were stationed in Vietnam and came into contact with "Agent Orange", a herbicide mixture of 2,4,5-T and 2,4-D. The exposed mothers were defined as women who lived with their families in areas sprayed with 2,4,5-T. In these studies simultaneous exposure of the fathers cannot be excluded.

Most of the available studies are inadequate as a result of methodological shortcomings or because they have insufficient statistical power because the collectives were too small. Some unpublished studies are only known from secondary sources and are not dealt with here, others are only available as abstracts. Positive results can therefore only be regarded as suggestive evidence, negative results do not exclude potential effects.

It must be noted that exposure is never to 2,4,5-T alone, but usually to a mixture of 2,4,5-T with other chemicals, in the case of "Agent Orange" with 2,4-D, and in particular with the impurity TCDD. The level of exposure to other chemicals and pesticides was determined in very few studies. Exposure criterion was usually the spraying of 2,4,5-T in a certain area, sometimes attempts were also made to quantify the amount sprayed. In no study was it checked that the individuals were actually exposed and in no study were the levels of exposure determined by analyzing blood or urine. It can be assumed that the aerosol exposure of herbicide sprayers is higher than that of persons that live in the areas sprayed.

Table 1. Studies and reports on the effects in children of exposure of fathers or mothers to 2,4,5-T

Type of study, criteria; substances investigated	End-points recorded	Results	References
Exposure of fathers			
case-control study, Australia, cases: 329 children controls: 328 children; exposure: "Agent Orange" during military service in Vietnam	structural defects	OR[1] (95 % CI[2]) 1.02 (0.78–1.32)	Donovan *et al*. 1984
case-control study, USA, cases: 7133 children controls: 4246 children; exposure: "Agent Orange" during military service in Vietnam	all congenital defects 2nd child with defects spina bifida harelip	OR (95 % CI) 0.97 (0.83–1.14) 2.57 (not specified) 1.19# (not specified) 1.07# (not specified) # *increased with increasing exposure, trend significant*	Erickson *et al*. 1984
cohort study, USA, exposed persons: 370 workers from chlorophenol production controls: 345 workers from other areas; exposure: TCDD (2,4,5-trichlorophenol production)	all lethal events still births spontaneous abortions cot deaths health effects congenital defects all findings together	OR (95 % CI) 1.02 (0.71–1.47) 0.97 (0.38–2.36) 0.96 (0.65–1.42) 0.82 (0.30–2.09) 0.93 (0.60–1.43) 1.08 (0.63–1.83) 0.98 (0.72–1.32)	Townsend *et al*. 1982
cohort study, New Zealand, exposed persons: 548 pesticide spayers controls: 441 farmers; exposure: 2,4,5-T herbicides	malformations miscarriages still births	RR[3] (90 % CI) 1.19 (0.58–2.45) 0.89 (0.61–1.30) 3/486 (lower than national incidence of 8.9/1000)	Smith *et al.* 1981b, 1982
Exposure of mothers			
case-control study, Arkansas, USA, cases: 1201 persons controls: local birth register; exposure: area planted with rice and sprayed with 2,4,5-T	harelip or cleft palate coloured women white women coloured men white men	incidence (per 1000 births) exposure low/medium/high 0.32 / 0.28 / **0.54*** 0.52 / 0.68 / 0.45 0.33 / 0.26 / 0.18 0.99 / 0.76 / 0.90 * p = 0.01 *effect attributed to different selection of cases*	Nelson *et al*. 1979
case-control study, New Brunswick, Canada, cases: 295 persons controls: groups of 2 from the birth register; exposure: areas sprayed with phenoxyacetic acid herbicides	still births, defects of the neural tube, facial clefts, kidney anomalies	no association (no other details) *time of pregnancy taken into account*	White *et al.* 1988

Table 1. continued

Type of study, criteria; substances investigated	End-points recorded	Results	References
cohort study, South Vietnam, 1965–1970 exposed persons: 7327 children from Than Phuong village controls: 6690 children from a district of Ho Chi Minh City; exposure: areas sprayed with "Agent Orange"	congenital anomalies (no other details) mole (completely degenerated embryo)	incidence (exposed persons/controls) 1.1 % / 0.43 % ($p < 0.005$) 0.73 % / 0.38 % ($p < 0.005$) *controls not comparable, "long-term effect" of TCDD investigated*	Phuong *et al*. 1989
cohort study, Northland, New Zealand, exposed persons: 9614 children (1972–1977) controls: 15000 children (1960–1966); exposure given as amount of 2,4,5-T used annually	all malformations cleft urethra clubfoot	IR[4] (90 % CI) **1.73*** (1.44–2.08 **5.62*** (2.69–11.73) **1.66*** (1.20–2.29) *time of pregnancy taken into account,* *selection effect possible*	Hanif *et al*. 1981
correlation study, Hungary, 1969–1976, incidence of congenital defects in the total population (about 10 million, about 25 % of these employed in agriculture or forestry); amount of 2,4,5-T used annually	amount of 2,4,5-T/ still births, spina bifida, anencephaly, facial clefts, cystic kidney diseases	no correlation *a large part of the population presumably exposed*	Thomas 1980 (abstract)
correlation study, New South Wales, Australia, 1965–1976, rate of defects of the neural tube in the regional population (about 5 million, 7.4 % of these employed in agriculture; Thomas 1980); amount of 2,4,5-T used annually	defects of the neural tube/ amount of 2,4,5-T up to 1974 (TCDD > 0.1 ppm) from 1975 (TCDD < 0.1 ppm) defects of the neural tube/time of use conception in summer conception in winter	positive correlation no correlation positive correlation no correlation	Field and Kerr 1979 (abstract)
2 case reports, agriculture; exposure: 2,4,5-T in the drinking water		meningomyelocele: 2 cases (frequent form of spina bifida) e*xposure during the first term of pregnancy*	Sare and Forbes 1972

[1] odds ratio, [2] confidence interval, [3] relative risk, [4] incidence

The parameters investigated were usually only malformations and still births, in some cases also miscarriages. Because of the results known from animal experiments, the malformations particularly taken note of were facial clefts, such as harelip and cleft palate, and defects of the neural tube, such as spina bifida (cleft spine), anencephaly (missing skull cap and most of the brain) or hydrocephalus (water on the brain). The possibility of an association with exposure during conception or pregnancy was only investigated in some studies. In addition, other possible reasons for the malformations (exposure to mixtures, other environmental influences) are only rarely considered.

Of the studies with exposure of the fathers to 2,4,5-T, TCDD and other substances, one valid study (Erickson *et al*. 1984) and other studies of limited validity (Donovan *et al*. 1984, Smith *et al*. 1981b, 1982, Townsend *et al*. 1982) yielded no evidence of an increase in the total incidence of structural malformations in children. The increased incidence of particular malformations such as spina bifida, anencephaly and facial clefts determined in the study of Erickson *et al*. (1984) cannot be considered proved because the study has inadequate resolving power for these malformations.

Two case-control studies of limited relevance and a study only available as an abstract, which were all carried out in agricultural areas, demonstrated no increase in the risk of facial clefts (Nelson *et al*. 1979, White *et al*. 1988), still births (Hanif *et al*. 1981, Thomas 1980, White *et al*. 1988), or defects of the neural tube or kidney damage (Thomas 1980, White *et al*. 1988) after exposure of the mothers. On the other hand, 2 cases of meningomyelocele, the most frequent form of spina bifida, were reported after suspected high exposure of the mothers to 2,4,5-T in the drinking water. Exposure occurred in both cases during the first trimester of pregnancy (Sare and Forbes 1972). A cohort study on the agricultural use of 2,4,5-T revealed an increase in the incidence of cleft urethra in males and clubfoot (Hanif *et al*. 1981); however, because of a selection effect the control group in this study is not comparable with the exposed group. In a cohort study in which the long-term effects of "Agent Orange" and in particular of TCDD were investigated, the overall incidence of congenital anomalies was increased (Phuong *et al*. 1989), but no attempt was made to differentiate between individual anomalies. In this study the urban control group is probably not comparable with the exposed rural group. In an abstract a positive correlation is described between the occurrence of defects of the neural tube and the use of 2,4,5-T. In particular the occurrence of defects of the neural tube correlated with conception in summer, the time of year when 2,4,5-T was used, and with the use of 2,4,5-T highly contaminated with TCDD (Field and Kerr 1979).

The available data indicate that after agricultural use of 2,4,5-T there is no marked increase in the incidence of malformations or still births. Suspected toxic effects on reproduction after supposed high maternal exposure to 2,4,5-T or 2,4,5-T highly contaminated with TCDD, can, however, not be disproved.

3.4 Carcinogenicity

Epidemiological studies have investigated the occurrence of tumours in workers from factories producing and processing 2,4,5-trichlorophenol (including production of

2,4,5-T herbicides). These cohorts were selected in particular because of simultaneous high exposure to TCDD as a result of accidents or unfavourable production processes. These studies are presented in the MAK Documentation for TCDD (Greim 1993). In these studies the total incidence of tumours and the incidence of lung tumours were increased. In some cases there was also an increase in soft-tissue sarcoma and tumours of the haematopoietic system.

In addition there are numerous other studies of persons exposed to 2,4,5-T and its impurity TCDD and also to other herbicides such as 2,4-D or 4-chloro-2-methylphenoxyacetic acid (MCPA) as a result of spraying herbicides in agriculture or in Vietnam (Greim 1993). Several cohort studies found an increased lung cancer risk which could not be explained by smoking alone. Some case-control studies revealed increased risks of developing very rare tumours such as soft-tissue sarcomas, non-Hodgkin's lymphomas or Hodgkin's lymphomas after exposure to herbicides which, in the case of 2,4,5-T herbicides, are contaminated with TCDD.

In a cohort study published in 1994, no significant increase in mortality (standard mortality ratio (SMR) 0.84; 95 % confidence interval (CI) 0.75–0.94) or in the tumour incidence (SMR 0.83; 95 % CI 0.65–1.02) was found in 1909 herbicide users exposed between 1955 and 1971 for at least 2 weeks to 2,4-D and 2,4,5-T. Mortality (with a latency period of 15 years) from pancreas tumours (SMR 1.17; 95 % CI 0.32–3.0), thyroid gland tumours (SMR 6.49; 95 % CI 0.17–36.2), lymphatic leukaemia (SMR 1.46; 95 % CI 0.04–8.11) or myeloid leukaemia (SMR 1.25; 95 % CI 0.03–6.96) was not significantly increased, but increased with increasing latency period. One person developed non-Hodgkin's lymphoma (standard incidence rate (SIR) 0.42; 95 % CI 0.01–2.35) after a latency period of 10 years and two people Hodgkin's lymphoma (SIR 1.18; 95 % CI 0.03–6.56 and SIR 1.89; 95 % CI 0.05–10.5) after latency periods of 10 and 15 years, respectively. Investigation of the herbicides used in the 1960s revealed contamination with TCDD at levels up to 1000 ppb. The authors conclude that there is no significantly increased risk of developing cancer after spraying 2,4-D or 2,4,5-T, but draw attention to the low statistical power of this study, which does not allow exclusion of carcinogenicity (Asp *et al*. 1994).

As a result of the exposure to mixtures and in particular of the sometimes very high contamination with TCDD in earlier years (unlike 2,4,5-T, TCDD has been found to be carcinogenic in animal experiments), no statement can be made as to the carcinogenic effects of 2,4,5-T in man from the studies described. There are no epidemiological studies of workers exposed to 2,4,5-T without or with only low simultaneous exposure to TCDD.

4 Animal Experiments and in vitro Studies

4.1 Acute toxicity

4.1.1 Inhalation

After inhalation exposure of male and female rats for one and four hours to aerosols of 2,4,5-T and two 2,4,5-T esters (mixed butyl ester and 2-ethylhexyl ester) at the highest possible concentrations (830, 1200 and 1100 mg/m^3, respectively) merely a transient decline in well-being was observed. No deaths occurred (DFG 1982).

4.1.2 Ingestion

After oral administration of 2,4,5-T, LD_{50} values were obtained for rats in the range from 500 to 750 mg/kg body weight. Mice and guinea pigs were found to be similarly sensitive with LD_{50} values of 400 to 800 mg/kg body weight, and the dog was the most sensitive species with an LD_{50} value of 100 mg/kg body weight. Symptoms included stiffleggedness, myotonia, reduced motor activity, ataxia and weight loss. Pathological changes were lung oedema, fatty degeneration of the liver and liver necrosis, degeneration of the epithelial cells of the kidney tubules and inflammation of the intestine (DFG 1982). LD_{50} values in the range from 700 to 1000 mg/kg body weight were found for various esters and salts of 2,4,5-T (DFG 1982).

4.1.3 Dermal absorption

With LD_{50} values of over 5000 mg/kg body weight, 2,4,5-T, the dimethylamine salt and the amyl ester, mixed butyl ester and 2-ethylhexyl ester were found to be of low toxicity after dermal application (DFG 1982).

4.2 Subacute, subchronic and chronic toxicity

The target organs of the toxic effects of 2,4,5-T in the rat are the kidneys and liver (Table 2). Medium-term and long-term feeding studies with 2,4,5-T contaminated with very low-levels of TCDD (< 0.33 ppb) revealed increases in the relative kidney weights and deposits in the kidneys after doses of 30 mg/kg body weight and more. Increased excretion of porphyrin was observed after doses of 10 mg/kg body weight and more. The NOEL was given as 3 mg/kg body weight (Kociba *et al*. 1979). In another long-term feeding study with 2,4,5-T administered for 30 months, no toxicologically relevant findings were observed up to the highest dose of 30 mg/kg body weight despite high-level

contamination with TCDD (50 ppb) (Celamerck 1979). In a study with 5-week administration of 2,4,5-T there was a reduction in the total leukocyte count from doses of 60 mg/kg body weight (Mirvish *et al*. 1991). Slight histological changes in the liver were found after 100 mg/kg body weight (DOW 1970, cited from FAO/WHO 1976).

Atrophy of the thyroid gland and spleen, and hypocellularity of the bone marrow and the lymph nodes were observed in female NCTR mice even at the lowest dose of 30 mg/kg body weight after oral administration of a technical grade 2,4,5-T preparation (50 ppb TCDD) for 5 days. In CD-1 mice these effects were not observed after exposure to the purified preparation (5 ppb TCDD) at the lowest dose of 60 mg/kg body weight. At this dose one case of hyperplasia of the thyroid gland was observed and after 120 mg/kg body weight one case of cortical atrophy of the thymus. Animals that were not pregnant reacted more sensitively than pregnant animals (Highman *et al*. 1976a, 1976b).

Dogs were found to be more sensitive than rats and mice. After oral administration of doses of 2,4,5-T of 20 mg/kg body weight for 13 weeks, probably with high-level contamination with TCDD, all the animals died. The symptoms included weakness, difficulties in swallowing and stiffness of the hind limbs. Doses up to 10 mg/kg, however, did not produce specific symptoms (Drill and Hiratzka 1953). In another study the only effect found after administration of 2,4,5-T doses of 2.4 and 13.3 mg/kg body weight for 3 months was an increase in the glutamate pyruvate transaminase values (Beraterforum für Präventivmedizin und Umweltschutz 1977); this result could not be reproduced in a follow-up study (Leuschner 1980, cited from DFG 1982). The NOEL was given as 2.4 mg/kg body weight.

Reduced body weights and vomiting were observed in Rhesus monkeys given 2,4,5-T doses of 12 mg/kg body weight for 18 days (Dougherty *et al*. 1975).

There are two medium-term studies in which 2,4,5-T esters were given to rats; there is, however, no data for the level of contamination with TCDD. With a mixed butyl ester, there were effects on the liver after 5 weeks at 30 mg/kg body weight, after 80 mg/kg body weight mainly effects on the thyroid gland and after 200 mg/kg body weight effects on the liver, kidneys, pancreas and salivary gland (Boehringer 1970b, cited from DFG 1982). Administration of a mixture of monopropylene, dipropylene and tripropylene glycol ethyl esters produced no toxic effects with doses up to 18.6 mg/kg body weight for 90 days; after 62 mg/kg body weight swelling of the liver and kidneys occurred (DOW 1961, cited from FAO/WHO 1976).

4.3 Local effects on skin and mucous membranes

2,4,5-T does not have irritative effects on rabbit skin, but is strongly irritative in the rabbit eye (DFG 1982). The moistened dimethylamine salt produced mild erythematous and oedematous changes only on scarified skin, but not on intact skin. In the rabbit eye it caused mild to marked conjunctivitis, and one of the three rabbits developed irreversible progressive clouding of the cornea (DFG 1982). The amyl ester led to increased desquamation and mild reddening and swelling of the skin and eyes (DFG 1982). The mixed butyl ester and ethylhexyl ester produced mild irritation of the skin and moderate mucosal irritation of the eye (DFG 1982).

Table 2. Multiple oral doses of 2,4,5-T and its compounds

Species, strain number, sex	Administration (duration, dose; route)	Substance (level of TCDD)	Effects	References
rat, Wistar groups of 4 ♀	5 weeks; 15, 30, 60, 120 mg/kg body weight; in the diet	2,4,5-T (3.3 ppb)	**from 60 mg/kg** body weights decreased, slight decrease in total leukocyte counts **120 mg/kg** decrease in total leukocyte counts	Mirvish *et al.* 1991
rat, RW-49 groups of 10 ♂/♀	5 weeks; 30, 80, 200 mg/kg body weight; gavage (emulsion in water)	2,4,5-T mixed butyl ester (TCDD not specified)	**30 mg/kg** "liver findings" in 2 animals **from 80 mg/kg** body weights decreased, decrease in food consumption, isolated deaths, decrease in thyroid gland weights, follicle epithelial hyperplasia or degeneration and reduction of colloid formation in the thyroid gland, increase in glutamate pyruvate transaminase and alkaline phosphatase, blood urea nitrogen values increased, specific urine weights decreased **200 mg/kg** increase in liver and kidney weights, fatty degeneration and necrosis of the liver, parenchymal damage in the kidneys, pancreas and salivary glands	Boehringer 1970b, cited from DFG 1982
rat, not specified groups of 10 ♂/♀	90 days; 3, 10, 30 100 mg/kg body weight; in the diet	2,4,5-T (< 1000 ppb)	**up to 10 mg/kg** no effects **from 30 mg/kg** slight changes **100 mg/kg** body weights decreased, decrease in food consumption, slight histological liver changes, increase in alkaline phosphatase	DOW 1970, cited from FAO/WHO 1976
rat, not specified groups of 10 ♂/♀	90 days 6.2, 18.6, 62, 186 mg/kg body weight; in the diet; as acid equivalent	mixture of 2,4,5-T monopropylene, dipropylene and tripropylene glycol ether ester (TCDD not specified)	**up to 18.6 mg/kg** no substance-related effects **from 62 mg/kg** swelling in the liver and kidneys; ♂: disturbances in growth, enlarged livers, increase in kidney weights, increase in alkaline phosphatase	DOW 1961, cited from FAO/WHO 1976

Table 2. continued

Species, strain number, sex	Administration (duration, dose; route)	Substance (level of TCDD)	Effects	References
rat, SD[1] groups of 10 ♂/♀	13 weeks 3, 10, 30 mg/kg body weight; in the diet	2,4,5-T (< 0.33 ppb)	**3 mg/kg** NOEL **from 10 mg/kg** ♂: increase in excretion of coproporphyrin **30 mg/kg** ♂: increase in excretion of uroporphyrin and coproporphyrin, increase in relative kidney weights; ♀: body weights decreased, increase in excretion of coproporphyrin, mineral deposits in the kidneys	Kociba *et al.* 1979
rat, SD groups of 50 ♂/♀	2 years 3, 10, 30 mg/kg body weight; in the diet	2,4,5-T (< 0.33 ppb)	**3 mg/kg** NOEL **from 10 mg/kg** ♀: mineral deposits in the kidneys; ♂: increase in excretion of coproporphyrin **30 mg/kg** body weights decreased, increase in relative kidney weights, increase in excretion of urine; ♂: increase in excretion of uroporphyrin; ♀: frequent deposits of pigment in cytoplasm of the kidney tubules, dilated heart ventricle	Kociba *et al.* 1979
rat, SD groups of 50 ♂/♀	30 months 3, 10, 30 mg/kg body weight; exposure in utero and via lactation, from week 6 in the diet	2,4,5-T (50 ppb)	**up to 30 mg/kg** no toxicologically-relevant findings (regarding clinical symptoms, clinico-chemical parameters and complete histopathological examination)	Leuschner *et al.* 1979
mouse, various strains, groups of 3–39 ♂/♀ (not pregnant or pregnant)	5–7 days 30 to 140 mg/kg body weight; oral	2,4,5-T pure (< 5 ppb) or technical grade (< 50 ppb)	**30 mg/kg (technical grade)** atrophy of the thyroid gland and spleen, hypocellularity of the bone marrow and lymph nodes, **from 60 mg/kg (pure**) hyperplasia of the thyroid gland, cortical atrophy of the thymus (only pregnant animals) **120 mg/kg (pure)** cortical atrophy of the thymus (also non-pregnant animals)	Highman *et al.* 1976a, 1976b

Table 2. continued

Species, strain number, sex	Administration (duration, dose; route)	Substance (level of TCDD)	Effects	References
dog, beagle groups of 4 ♂/♀	13 weeks 0.5, 2.4, 13.3 mg/kg body weight; in the diet	2,4,5-T (TCDD not specified)	**0.5 mg/kg** decrease in serum creatinine **from 2.4 mg/kg** glutamate pyruvate transaminase values decreased, no pathomorphological findings	Beraterforum für Präventiv-medizin und Umweltschutz (1977)
dog, beagle not specified	3 months 0.1, 0.5, 2.4 mg/kg body weight; in the diet	2,4,5-T (TCDD not specified)	**up to 2.4 mg/kg** NOEL (no effects on clinico-chemical parameters)	Leuschner 1980, cited from DFG 1982
dog, mongrel groups of 2–4	13 weeks 2, 5, 10, 20 mg/kg body weight; oral, capsules	2,4,5-T (TCDD not specified)	**up to 10 mg/kg** no significant substance-related effects (regarding general symptoms, haematology, organ weights, autopsy, histopathology) **20 mg/kg** all animals died, mild congestion of the liver and liver necrosis, symptoms: weakness, difficulties in swallowing, stiffness of the hind limbs	Drill and Hiratzka 1953
monkey, Rhesus 40 ♀	18 days 12 mg/kg body weight; oral, capsules	2,4,5-T (50 ppb)	**12 mg/kg** vomiting, body weights decreased	Dougherty *et al.* 1975

[1] Sprague-Dawley

4.4 Allergenic effects

There are no valid investigations on the allergenic effects of 2,4,5-T.

In a study with guinea pigs published in 1960, no evidence of an allergenic potential of 2,4,5-T was found (DFG 1982).

4.5 Reproductive toxicity

Numerous studies of the reproductive toxicity and in particular teratogenic effects of 2,4,5-T have been carried out with mice, rats, hamsters, rabbits and monkeys. These studies are presented in detail in Table 3. As most of the 2,4,5-T samples used were contaminated with TCDD, which is highly embryotoxic, the studies are listed in the order of the TCDD level in the 2,4,5-T samples. The studies relevant for the present evaluation are also listed in Tables 4 to 6 giving the no effect levels and the lowest concentrations with effects. To estimate the influence of TCDD, studies are also included which were carried out with TCDD alone.

4.5.1 Fertility

Doses of 2,4,5-T or its isooctyl ester of 200 mg/kg body weight led to a significant inhibition of testicular DNA synthesis (Seiler 1979).

In a 3-generation study with rats with a 2,4,5-T sample which contained less than 0.03 ppb TCDD, fertility was reduced only after 10 mg/kg body weight in the F_3 generation, but not after 3 or 30 mg/kg body weight or in the other generations. The authors therefore regard this as an incidental finding (Smith *et al*. 1981a).

A dominant lethal test, in which female rats were fed 2,4,5-T containing 50 ppb TCDD for 8 weeks in daily doses of 0.1 to 10 mg/kg body weight, yielded no evidence of effects on female fertility (see Table 8, Herbold *et al*. 1982). In a dominant lethal test with male mice given a single intraperitoneal dose of 100 mg 2,4,5-T with an unknown level of TCDD, no effects were found on male fertility or on embryogenesis (see Table 8, Buselmaier *et al*. 1972).

4.5.2 Multi-generation studies

No toxic effects on reproduction were found in one of two 3-generation studies with rats given 2,4,5-T doses of 3, 10 and 30 mg/kg body weight (Table 4; Celamerck 1978). In the other study in which the 2,4,5-T had very low-level contamination with TCDD, effects on prenatal and postnatal survival were observed (Table 4; Smith *et al*. 1981a). After 2,4,5-T doses of 3 and 10 mg/kg body weight survival was reduced in some groups, after 30 mg/kg body weight survival was reduced in all generations. The authors regard 2,4,5-T doses of 3 and 10 mg/kg body weight as not having toxic effects on reproduction, 30 mg/kg body weight as producing reproductive toxicity reflected in reductions in postnatal survival. Maternal toxicity was not found in any of the studies (Table 3).

Table 3. Effects of 2,4,5-T compounds on reproduction

Species, strain number, sex	Administration (dose, duration; route)	Substance (level of TCDD)	Effects	References
mouse, CD-1 groups of at least 8 ♀	1 × 800–900 mg/kg body weight between days 8 and 15 of gestation or 3 × 250–300 mg/kg body weight on days 7–9, 10–12 or 13–15 of gestation; oral	2,4,5-T (10 ppb and < 1 ppb)	**A total of 800–900 mg/kg** F_0: no details; F_1: foetal weights decreased (after treatment on days 14, 15), increase in foetal mortality, resorptions (after treatment on days 11, 14, 15), increase in malformations (after a single dose on days 10, 11 or 12 or after three doses on days 13–15), increase in skeletal malformations (after treatment on days 13–15), increase in cleft palate (after a single dose on days 9–14 or 3 doses on days 10–12 or 13–15)	Hood *et al*. 1979
mouse, NMRI groups of 7–35 ♀	8, 15, 30, 45, 60, 90, 120 mg/kg body weight on days 6–15 of gestation; oral, gavage	2,4,5-T (< 20 ppb)	**8 mg/kg** F_1: no effects **from 15 mg/kg** F_1: foetal weights decreased **from 45 mg/kg** F_1: increase in cleft palate **from 60 mg/kg** F_1: increase in resorptions **from 90 mg/kg** F_0: body weights decreased	Neubert and Dillmann 1972
mouse, A/J C57BL/6, C3H/He, BALB/c, CD-1 groups of at least 11 ♀	15, 20, 25, 30, 45, 60, 75, 90 mg/kg body weight on days 6–14 of gestation; oral, gavage	2,4,5-T, technical grade (50 ppb)	**from 30 mg/kg** F_1: foetal weights decreased (A/J, BALB/c, CD-1), increase in resorptions and cleft palate (A/J) **from 45 mg/kg** F_1: foetal weights decreased (C3H/He), increase in foetal mortality (A/J), increase in resorptions and cleft palate-(CD-1) **from 60 mg/kg** F_1: foetal weights decreased (C57/BL/6), increase in resorptions (BALB/c), increase in cleft palate (C57BL/6, BALB/c) **from 75 mg/kg** F_1: increase in foetal mortality (BALB/c, CD-1), increase in resorptions (C57BL/6) **90 mg/kg** F_1: increase in foetal mortality (C57BL/6, C3H/He), increase in resorptions and cleft palate (C3H/He)	Holson *et al*. 1992

Table 3. continued

Species, strain number, sex	Administration (dose, duration; route)	Substance (level of TCDD)	Effects	References
mouse, CD-1 groups of at least 5 ♀	115 mg/kg body weight on days 10–15 of gestation; oral 200 mg/kg body weight on days 11–13/14 of gestation; oral 255 mg/kg body weight on days 12–15 of gestation; oral	2,4,5-T (< 50 ppb)	**115 mg/kg** F_0: relative liver weights slightly increased (not significant); F_1: no effects **200 mg/kg** F_0: relative liver weights increased; F_1: increase in foetal mortality only in those animals treated on days 11 to 14	Courtney 1977
mouse, CD-1 DBA/J2, C57Bl/6J groups of 3–15 ♀	100, 125 mg/kg body weight on days 6–15 of gestation; subcutaneous	2,4,5-T (< 50 ppb)	**from 100 mg/kg** F_0: relative liver weights increased; F_1: foetal weights decreased, increase in cleft palate and kidney anomalies (not significant)	Courtney and Moore 1971
mouse, NMRI groups of 21–35 ♀	20, 35, 60 90, 130 mg/kg body weight on days 6–15 of gestation; oral, gavage	2,4,5-T (50 ppb)	**20 mg/kg** F_1: foetal weights decreased **from 35 mg/kg** F_1: increase in cleft palate **from 90 mg/kg** F_0: body weights decreased; F_1: decrease in implantations **130 mg/kg** F_0: increase in mortality; F_1: increase in resorptions, dead foetuses	Roll 1971
mouse, NMRI not specified	20, 40, 80 120 mg/kg body weight on days 6–15 of gestation; oral, gavage	2,4,5-T (< 100 ppb)	**20 mg/kg** F_0: no maternal toxicity; F_1: no foetal toxicity **40 mg/kg** F_0: no maternal toxicity; F_1: foetal weights and lengths decreased **from 80 mg/kg** F_0: body weights decreased; F_1: foetal weights and lengths decreased, increase in cleft palate	Merck 1972a
mouse, NMRI not specified	40, 80 120 mg/kg body weight on days 6–15 of gestation; oral, gavage	2,4,5-T (< 100 ppb)	**40 mg/kg** F_0. no maternal toxicity; F_1: no foetal toxicity **80 mg/kg** F_0: no maternal toxicity; F_1: slightly delayed foetal development, foetal weights and lengths decreased; non-significant increase in cleft palate **120 mg/kg** F_0: maternal toxicity; F_1: lethal effects on foetuses, teratogenic effects (mainly cleft palates)	Merck 1972b

Table 3. continued

Species, strain number, sex	Administration (dose, duration; route)	Substance (level of TCDD)	Effects	References
mouse, CD-1 DBA/J2, C57Bl/6J groups of 3–15 ♀	50, 100, 150 mg/kg body weight on days 6–15 of gestation; subcutaneous	2,4,5-T, technical grade (500 ppb)	**50 mg/kg** F_0: no maternal toxicity; F_1: no embryotoxic or teratogenic effects **from 100 mg/kg** F_0: relative liver weights increased; F_1: foetal weights decreased, increase in cleft palate and kidney anomalies (not significant)	Courtney and Moore 1971
mouse, CD-1 groups of 25 and 29 ♀	20, 100 mg/kg body weight on days 6–15 of gestation; oral	2,4,5-T (< 500 ppb)	**from 20 mg/kg** F_0: no details; F_1: increase in atypical foetuses, increase in still births **100 mg/kg** F_0: deaths (7/29); F_1: foetal weights decreased, increase in skeletal variations	Beck 1981
mouse, C57BL/6, AKR groups of 6–18 ♀	C57BL/6: 21.5, 113 mg/kg body weight (DMSO) on days 6–14 of gestation; oral 46.4, 113 mg/kg body weight (honey); oral AKR: 113 mg/kg body weight (DMSO or honey) on days 6–15 of gestation; oral	2,4,5-T (30000 ppb)	**21 mg/kg (in DMSO)** F_1: no effects **46.4 mg/kg (in honey)** F_1: increase in abnormal foetuses, increase in kidney cysts **113 mg/kg (in DMSO or honey)** F_0: liver weights increased; F_1: relative foetal liver weights increased, foetal weights decreased, increase in foetal mortality, increase in cleft palate and kidney cysts	Courtney *et al*. 1970
mouse, NMRI groups of 4 ♀	20, 40, 80, 120, 160 mg/kg body weight on days 6–15 of gestation; oral as acid equivalent	2,4,5-T diethylamine salt herbicide (TCDD not specified)	**up to 40 mg/kg** F_0: no maternal toxicity; F_1: no foetal toxicity **from 80 mg/kg** F_0: no maternal toxicity; F_1: foetal weights decreased **from 120 mg/kg** F_0: increase in resorptions, increase in runts, weakly teratogenic **160 mg/kg** F_0: highly teratogenic	Celamerck 1974d

Table 3. continued

Species, strain number, sex	Administration (dose, duration; route)	Substance (level of TCDD)	Effects	References
mouse, NMRI groups of 25 ♀	20, 40, 80, 120, 160 mg/kg body weight on days 6–15 of gestation; oral as acid equivalent	2,4,5-T diethylamine salt (without formulation aids) (TCDD not specified)	**up to 40 mg/kg** F_0: no maternal toxicity; F_1: no foetal toxicity **from 80 mg/kg** F_0: no maternal toxicity; F_1: foetal weights deceased **from 120 mg/kg** F_0: body weights decreased, deaths; F_1: increase in resorptions, increase in abortion, increase in runts, mildly teratogenic (mainly cleft palates) **160 mg/kg** F_1: highly teratogenic (mainly cleft palates)	Celamerck 1975a
mouse, NMRI not specified	87, 219, 374 mg/m^3 for 5 hours/day on days 6–15 of gestation; inhalation as acid equivalent	2,4,5-T diethylamine salt (TCDD not specified)	**87 mg/m^3** F_0: no maternal toxicity; F_1: foetal weights decreased **219 mg/m^3** F_0: no maternal toxicity; F_1: foetal weights decreased, increase in resorptions and cleft palate **374 mg/m^3** F_0: high maternal toxicity; F_1: embryotoxic and foetotoxic	Celamerck 1975b
mouse, NMRI groups of 15 to 19 ♀	85, 216, 374 mg/m^3 for 5 hours/day on days 6–15 of gestation; inhalation as acid equivalent	2,4,5-T butoxy ethyl ester (TCDD not specified)	**85 mg/m^3** (about 600 µg/mouse, about 15 mg/kg body weight) F_0: no maternal toxicity; F_1: no embryotoxicity **from 216 mg/m^3** F_0: slight maternal toxicity; F_1: foetal deaths, increase in cleft palate **374 mg/m^3** F_0: maternal mortality; F_1: increase in abortions and resorptions	Celamerck 1974a
mouse, NMRI not specified	20, 40, 80, 120, 160, 200 mg/kg body weight on days 6–15 of gestation; oral as acid equivalent	2,4,5-T butoxy ethyl ester herbicide (TCDD not specified)	**up to 40 mg/kg** F_0: no maternal toxicity; F_1: no foetal toxicity **from 80 mg/kg** F_0: no maternal toxicity; F_1: foetal weights decreased, foetal lengths decreased **from 120 mg/kg** F_0: body weights decreased, deaths; F_1: delayed foetal development, increase in cleft palate **from 160 mg/kg** F_0: body weights decreased, symptoms of intoxication, deaths; F_1: increase in abortions, resorptions and malformations, retardation	Celamerck 1974b, 1974c
mouse, NMRI groups of at least 18 ♀	50, 110 mg/kg body weight on days 6–14 of gestation; subcutaneous	2,4,5-T butoxy ethyl ester (< 1000 ppb)	**50 mg/kg** F_1: increase in resorptions and cleft palate **110 mg/kg** F_0: no details; F_1: increase in foetal mortality, foetal weights decreased	Båge *et al.* 1973

Table 3. continued

Species, strain number, sex	Administration (dose, duration; route)	Substance (level of TCDD)	Effects	References
mouse, NMRI groups of 9 ♀	12, 74 mg/kg body weight on days 6–15 of gestation; oral, gavage	2,4,5-T-butylester (TCDD not specified)	**12 mg/kg** F_1: foetal weights decreased **74 mg/kg** F_0: no details; F_1: increase in cleft palate	Neubert and Dillmann 1972
mouse, CD-1 groups of at least 6 ♀	115 mg/kg body weight on days 7/10–15 of gestation; oral 200 mg/kg body weight on days 11–13 of gestation; oral 255 mg/kg body weight on days 12–15 of gestation; oral as acid equivalent	2,4,5-T *n*-butylester (< 100 ppb)	**115 mg/kg** F_0: relative liver weights increased (only after exposure on days 7–15); F_1: no effects **200 mg/kg** F_0: no effects; F_1: foetal weights decreased **255 mg/kg** F_0: relative liver weights increased; F_1: increase in foetal deaths, foetal weights decreased, slight increase in cleft palate	Courtney 1977
mouse, CD-1 groups of at least 4 ♀	115 mg/kg body weight on days 7/10–15 of gestation; oral 200 mg/kg body weight on days 11–13 of gestation; oral 255 mg/kg body weight on days 12–15 of gestation; oral as acid equivalent	2,4,5-T isooctyl ester (< 100 ppb)	**115 mg/kg** F_0: relative liver weights increased (only after exposure on days 7–15); F_1: foetal weights decreased (only after exposure on days 7–15) **200 mg/kg** F_0: relative liver weights increased; F_1: no effects **255 mg/kg** F_0: relative liver weights increased; F_1: increase in foetal deaths, foetal weights decreased, slight increase in cleft palate	Courtney 1977

Table 3. continued

Species, strain number, sex	Administration (dose, duration; route)	Substance (level of TCDD)	Effects	References
mouse, CD-1 groups of at least 8 ♀	115 mg/kg body weight on days 7/10–15 of gestation; oral 255 mg/kg body weight on days 12–15 of gestation; oral as acid equivalent	2,4,5-T PGBE[1] (< 500 ppb)	**115 mg/kg** F_0: relative liver weights increased; F_1: no effects **255 mg/kg** F_0: relative liver weights increased; F_1: increase in foetal deaths, foetal weights decreased, slight increase in cleft palate	Courtney 1977
rat, SD groups of at least 10 ♂, 20 ♀	3 generations 3, 10, 30 mg/kg body weight; in the diet	2,4,5-T (< 0.03 ppb)	**3 mg/kg** F_1: decrease in perinatal and postnatal survival **10 mg/kg** F_2: decrease in postnatal survival; F_{2b}: reduced fertility **30 mg/kg** F_0: no maternal toxicity; F_1: decrease in perinatal and postnatal survival; F_2: liver weights increased, decrease in perinatal and postnatal survival; F_3: liver weights increased, thymus weights decreased, decrease in postnatal survival	Smith *et al.* 1981a
rat, SD groups of 20 ♂/♀	3 generations 3, 10, 30 mg/kg body weight; in the diet	2,4,5-T (50 ppb)	**up to 30 mg/kg** F_0: no effects; $F_{1, 2, 3}$: no effects	Celamerck 1978
rat, FW-49 groups of 23 ♀	25, 50, 100, 150 mg/kg body weight on days 6–15 of gestation; oral, gavage	2,4,5-T, pure (< 20 ppb)	**25 mg/kg** F_1: no effects **50 mg/kg** F_0: no effects; F_1: increase in resorptions and no. of dead foetuses **from 100 mg/kg** F_0: increase in deaths, body weights decreased; F_1: foetal weights decreased	Boehringer 1970a
rat, FW-49 groups of 23 ♀	25, 50, 75, 100 mg/kg body weight on days 6–15 of gestation; oral, gavage	2,4,5-T, technical grade (80 ppb)	**25 mg/kg** F_1: no effects **50 mg/kg** F_0: no effects; F_1: increase in resorptions and no. of dead foetuses **from 75 mg/kg** F_0: body weights decreased; F_1: foetal weights decreased, delays in growth and ossification **100 mg/kg** F_0: increase in deaths	Boehringer 1971

[1] Propylene glycol butyl ether ester

Table 3. continued

Species, strain number, sex	Administration (dose, duration; route)	Substance (level of TCDD)	Effects	References
rat, Wistar groups of at least 7 ♀	25, 50 100, 150 mg/kg body weight on days 6–15 of gestation; oral	2,4,5-T (< 500 ppb)	**up to 50 mg/kg** F_0: no apparent maternal toxicity; F_1: no embryotoxicity **100 mg/kg** F_0: no apparent maternal toxicity; F_1: increase in foetal deaths, foetal weights decreased, increase in skeletal malformations (particularly the breastbone), postnatal development unaffected **150 mg/kg** F_0: maternal body weights decreased, isolated deaths	Khera and McKinley 1972
rat, Wistar groups of at least 3 ♀	50, 150 mg/kg body weight on days 6–15 of gestation; oral	2,4,5-T butyl ester (< 500 ppb)	**150 mg/kg** F_0: no details; F_1: no significant effects (neither embryotoxic nor teratogenic nor postnatal toxic effects)	Khera and McKinley 1972
rat, SD groups of 25 ♀	1, 3, 6, 12, 24, 50, 100* mg/kg body weight on days 6–15 of gestation *(days 6–10 of gestation); oral	2,4,5-T (500 ppb)	**up to 50 mg/kg** F_0: no maternal toxicity; F_1: no embryotoxicity **100 mg/kg** F_0: maternal toxicity, deaths; F_1: foetal toxicity, foetal mortality, not teratogenic	Emerson *et al*. 1971; Thompson *et al*. 1971 (abstract)
rat, SD groups of 25 ♀	50, 100* mg/kg body weight on days 6–15 of gestation *(days 6–10 of gestation); oral	2,4,5-T (500 ppb)	**50 mg/kg** F_0: no maternal toxicity; F_1: slight, non-significant increase in resorptions, non-significant decrease in the number of implantations and *corpora lutea*, increase in anomalies (delayed ossification) **100 mg/kg** F_0: body weights decreased, deaths; F_1: increase in resorptions, foetal body weights decreased, weak ossification of the breastbone, delayed ossification, breastbone not properly joined	Parschu *et al*. 1971b
rat, CD groups of 8 ♀	10, 21, 46, 80 mg/kg body weight on days 6–15 of gestation; oral, gavage	2,4,5-T technical grade (500 ppb)	**from 46 mg/kg** F_0: body weights decreased; F_1: no effect on the development of newborn rats **80 mg/kg** F_0: relative liver weights increased; F_1: non-significant increase in foetal deaths, not teratogenic	Courtney and Moore 1971
rat, not specified groups of at least 6 ♀	4.6, 10, 46.4 mg/kg body weight on days 10–15 of gestation; oral	2,4,5-T (30000 ppb)	**from 4.6 mg/kg** F_1: increase in abnormal foetuses, haemorrhage of the gastrointestinal tract **from 10 mg/kg** F_0: no details; F_1: increase in mortality, increase in kidney cysts	Courtney *et al*. 1970

Table 3. continued

Species, strain number, sex	Administration (dose, duration; route)	Substance (level of TCDD)	Effects	References
hamster, Syrian groups of at least 7 ♀	40, 80, 100 mg/kg body weight on days 6–10 of gestation; oral	2,4,5-T, technical grade (< 100 ppb)	**40 mg/kg** F_1: no effects **from 80 mg/kg** F_1: increase in foetal mortality **100 mg/kg** F_0: no details; F_1: foetal weights decreased	Collins and Williams 1971
hamster, Syrian groups of at least 8 ♀	40, 80, 100 mg/kg body weight on days 6–10 of gestation; oral	2,4,5-T, recrystallized (< 100 ppb)	**40 mg/kg** F_1: increase in foetal mortality, foetal weights decreased **100 mg/kg** F_0: no details; F_1: increase in anomalies	Collins and Williams 1971
hamster, Syrian groups of at least 8 ♀	20, 40, 80, 100 mg/kg body weight on days 6–10 of gestation; oral	2,4,5-T, technical grade (500 ppb)	**20 mg/kg** F_1: increase in foetal mortality, foetal weights decreased **from 80 mg/kg** F_0: no details; F_1: increase in anomalies	Collins and Williams 1971
rabbit, New Zealand White groups of 20 ♀	10, 20, 40 mg/kg body weight on days 6–18 of gestation; oral	2,4,5-T (500 ppb)	**up to 40 mg/kg** F_0: no effects; F_1: not embryotoxic	Emerson *et al*. 1971
monkey, Rhesus groups of 10 ♀	0.05, 1, 10 mg/kg body weight on days 22–38 of gestation; oral	2,4,5-T (50 ppb)	**up to 10 mg/kg** F_0: no maternal toxicity; F_1: no embryotoxicity or postnatal toxicity (offspring observed for 1 year)	Dougherty *et al*. 1975
monkey, Rhesus groups of 4–5 ♀	5, 10, 20, 40 mg/kg body weight from day 20/22 of gestation for 4 weeks, 3 x/week; oral, gavage	2,4,5-T (< 100 ppb)	**up to 20 mg/kg** F_1: no effects **40 mg/kg** F_0: 1/5 animals aborted (possibly an incidental finding); F_1: tendency towards decreased foetal weights	Wilson 1971

Table 4. Toxic effects on reproduction after exposure of Sprague-Dawley rats to 2,4,5-T and TCDD in 3-generation studies

2,4,5-T*	TCDD*	Effects	References
–	1	NOAEL (marginal dilation of the renal pelvis in F_1)	Murray *et al*. 1979
–	10	reduced fertility in F_1 and F_2; reductions in litter size and reduced survival in F_1–F_3	Murray *et al*. 1979
–	100	fertility also reduced in F_0	Murray *et al*. 1979
3	< 0.00009	no dose-dependent effects (only in F_1 decrease in prenatal and postnatal survival)	Smith *et al*. 1981a
10	< 0.0003	no dose-dependent effects (only in F_2 decrease in postnatal survival)	Smith *et al*. 1981a
30	< 0.0009	decrease in prenatal survival in F_1–F_2 decrease in postnatal survival in F_1–F_3	Smith *et al*. 1981a
30	1.5	no effects	Celamerck 1978

* mg/kg body weight

4.5.3 Developmental toxicity

In studies with 2,4,5-T samples containing concentrations of TCDD which alone were insufficient to produce embryotoxic effects in comparable studies, reductions in foetal body weights occurred in mice in one study after 2,4,5-T doses as low 15 mg/kg body weight, in other studies from 20 or 40 mg/kg body weight. The incidence of cleft palate was increased after 2,4,5-T doses from about 30 mg/kg body weight (Tables 3 and 5). The NOEL in various studies was found to be 8, 20 and 40 mg/kg body weight. Maternally toxic effects were observed after 2,4,5-T doses of about 80 to 100 mg/kg body weight (Table 3; Beck 1981, Courtney and Moore 1971, Merck 1972a, Neubert and Dillmann 1972, Roll 1971). Effects similar to those caused by the acid were achieved with the esters and salts of 2,4,5-T, in the case of the butyl ester in the same dose range (Table 3; Neubert and Dillmann 1972), in the case of a butoxyethyl ester herbicide, a diethylamine salt herbicide and a diethylamine salt only after much higher doses (Table 3; Celamerck 1974b, 1974c, 1974d, 1975a). The mouse is regarded as a particularly sensitive species.

In rats, embryo mortality (increased resorption) and delayed ossification were observed from 2,4,5-T doses of 50 mg/kg body weight and skeletal malformation after 100 mg/kg body weight (Tables 3 and 6). Maternally toxic effects did not occur after 2,4,5-T doses of 50 mg/kg body weight. After 75 mg/kg body weight the body weights of the dams were found to be reduced in one study (Table 3; Boehringer 1971) and after 100 mg 2,4,5-T there were isolated deaths (Table 3; Boehringer 1971, Emerson *et al*. 1971, Parschu *et al*. 1971b).

Table 5. Toxic effects on reproduction after administration of 10 oral doses of 2,4,5-T and TCDD to female mice on days 6 to 15 of gestation

Strain of mouse	2,4,5-T*	TCDD*	Effects	References
CF-1	–	100	NOEL	Smith *et al*. 1976
NMRI	–	300	decreased foetal weights	Neubert and Dillmann 1972
CF-1	–	1000	increase in cleft palate	Smith *et al*. 1976
NMRI	–	3000	increase in cleft palate	Neubert and Dillmann 1972
NMRI	–	9000	increase in resorptions	Neubert and Dillmann 1972
NMRI	8	0.16	NOEL	Neubert and Dillmann 1972
NMRI	15	0.3	decreased foetal weights	Neubert and Dillmann 1972
NMRI	20	< 20	NOEL	Merck 1972a
NMRI	20	1.0	decreased foetal weights	Roll 1971
CD-1	20	10	increase in malformations and still births	Beck 1981
A/J C57/BL CD-1	30	1.5	decreased foetal weights, increase in cleft palate	Holson *et al*. 1992
NMRI	35	1.75	increase in cleft palate	Roll 1971
NMRI	40	< 40	NOEL	Merck 1972b
NMRI	40	< 40	decreased foetal weights	Merck 1972a
NMRI	45	0.9	increase in cleft palate	Neubert and Dillmann 1972

* mg/kg body weight

In rats, embryo mortality (increased resorption) and delayed ossification were observed from 2,4,5-T doses of 50 mg/kg body weight and skeletal malformation after 100 mg/kg body weight (Tables 3 and 6). Maternally toxic effects did not occur after 2,4,5-T doses of 50 mg/kg body weight. After 75 mg/kg body weight the body weights of the dams were found to be reduced in one study (Table 3; Boehringer 1971) and after 100 mg 2,4,5-T there were isolated deaths (Table 3; Boehringer 1971, Emerson *et al*. 1971, Parschu *et al*. 1971b).

Two studies with adequate statistical power were also carried out with Rhesus monkeys with relatively high numbers of animals (groups of 4–5 and groups of 10 animals/dose). After doses of 10 mg/kg body weight neither maternally toxic nor embryotoxic effects occurred (Table 3; Dougherty *et al*. 1975, Wilson 1971). After the highest dose of 40 mg/kg body weight there was, however, a slight tendency towards reduced foetal weights (Table 3; Wilson 1971).

Table 6. Toxic effects on reproduction after administration of 10 oral doses of 2,4,5-T and TCDD to female rats on days 6 to 15 of gestation

Strain of rat	2,4,5-T*	TCDD*	Effects	References
Sprague-Dawley	–	30	NOEL	Parschu *et al.* 1971a
Sprague-Dawley	–	125	decreased foetal weights, skeletal anomalies (incomplete ossification, wavy ribs) intestinal haemorrhages	Parschu *et al.* 1971a
Sprague-Dawley	–	500	foetal mortality, maternal toxicity	Parschu *et al.* 1971a
CD	46	23	NOEL	Courtney and Moore 1971
Wistar	50	< 25	NOEL	Khera and McKinley 1972
Sprague-Dawley	50	25	NOEL	Emerson *et al.* 1971
FW-49	50	< 10	increase in resorptions	Boehringer 1971
Sprague-Dawley	50	25	delayed ossification, slight increase in resorptions	Parschu *et al.* 1971b
Sprague-Dawley	80	40	slight increase in foetal mortality	Courtney and Moore 1971
Wistar	100	< 50	foetal mortality, skeletal malformations	Khera and McKinley 1972

* mg/kg body weight

4.6 Genotoxicity

4.6.1 *In vitro*

Classical genotoxicity tests with bacteria such as reversion tests (e.g. *Salmonella* mutagenicity test), the rec assay, DNA repair, the SOS chromotest and gene conversion tests with yeasts yielded negative results (Table 7). From test systems with mammalian cells there is evidence of effects on intercellular communication (Rubinstein *et al*. 1984) and an increase in sister chromatid exchange (Galloway *et al*. 1987) in the absence of a metabolizing system. After addition of an activating system a slight increase in the incidence of chromosomal aberration (Galloway *et al*. 1987) and the induction of prophages in *Escherichia coli* (George *et al*. 1992) were observed in the high dose range. The weak clastogenic effects observed after the addition of an activating system are probably caused by phenolic metabolites (Matsuoka *et al*. 1988). Positive results in genotoxicity tests could also be the result of the inhibition of DNA synthesis by 2,4,5-T demonstrated *in vitro* (Zhao *et al*. 1987).

Table 7. Genotoxicity of 2,4,5-T and its compounds *in vitro*

Test system	Substance (level of TCDD)	Maximum dose (effective dose –S9/+S9)	Result[1] –S9	+S9	Comments	References
Ames test *S. typhimurium* TA98, TA100, TA1535, TA1537	2,4,5-T (50 ppb)	2500 µg/plate	–	–		Herbold *et al.* 1982
Ames test *S. typhimurium* TA98, TA100, TA102, TA104	2,4,5-T (TCDD n.s.)	10000 µg/plate	–	–		George *et al.* 1992
Ames test *S. typhimurium* TA98, TA100, TA1535, TA1538	2,4,5-T (TCDD n.s.)	2500 µg/plate	–	–		Anderson and Styles 1978
Ames test *S. typhimurium* TA97, TA98, TA100, TA102	2,4,5-T (TCDD n.s.)	1000 µg/plate	–	–		Mersch-Sundermann *et al*. 1988
Ames test *S. typhimurium* TA97, TA98, TA100, TA1535, TA1537	2,4,5-T *n*-butyl ester isobutyl ester isooctyl ester (TCDD n.s.)	10000 µg/plate	–	–		Mortelmans *et al*. 1984
rec assay *B. subtilis* H17 Rec+ and M45 Rec–	2,4,5-T (TCDD n.s.)	n.s.	–			Shirasu *et al.* 1976
reversion *E. coli* WP2 *S. typhimurium*	2,4,5-T (TCDD n.s.)	n.s.	–			Shirasu *et al.* 1976
DNA repair *S. typhimurium* TA1538/ TA1978, *E. coli* K-12, *E. coli* WP_2	2,4,5-T (TCDD n.s.)	n.s.	–			Rashid and Mumma 1986
SOS chromotest *E. coli* PQ37	2,4,5-T (TCDD n.s.)	10000 µg/ml	–	–	toxic after 10 mg/ml	Mersch-Sundermann *et al.* 1989
reversion *Saccharomyces cerevisiae*	2,4,5-T (< 1000 ppb)	60 µg/ml	+?		positive after cytotoxic concentr-ations	Zetterberg 1978

Table 7. continued

Test system	Substance (level of TCDD)	Maximum dose (effective dose –S9/+S9)	Result[1] –S9	+S9	Comments	References
mitotic gene conversion *Saccharomyces cerevisiae*	2,4,5-T amyl ester (TCDD n.s.)	1000 µg/ml	–			Siebert and Lemperle 1974
prophage induction *E. coli* $WP2_S$ (λ)	2,4,5-T (TCDD n.s.)	100 µg/ml (–/100 µg/ml)	–	+		George *et al.* 1992
CA[2] CHO cells (Chinese hamster ovary cells)	2,4,5-T (TCDD n.s.)	2000 µg/ml (–/1500 µg/ml)	–	+	positive only after 29–37 hours	Galloway *et al.* 1987
SCE[3] CHO cells (Chinese hamster ovary cells)	2,4,5-T (TCDD n.s.)	5000 µg/ml (300/167 µg/ml)	+	+?	positive only after 26 hours	Galloway *et al.* 1987
inhibition of intercellular communication V79 cells (Syrian hamster fibroblasts)	2,4,5-T (23 ppb)	130 µg/ml (75 µg/ml)	+			Rubinstein *et al*. 1984

[1] + positive, +? questionably positive, – negative
[2] chromosomal aberration
[3] sister chromatid exchange
n.s. not specified

4.6.2 *In vivo*

In vivo investigations such as the dominant lethal test, host-mediated assay, micronucleus test, chromosomal aberration test with 2,4,5-T and the host-mediated assay with the *n*-butyl ester yielded negative results in mice (Table 8). A chromosomal aberration test with a 2,4,5-T butoxyethyl ester herbicide revealed a clastogenic effect, which, however, was also seen with the solvent and emulsifier alone.

With *Drosophila melanogaster* both positive and negative results were produced; the positive effects were weak (three times the control values at most) and only observed after high doses (1000 µg/ml).

Table 8. Genotoxicity of 2,4,5-T and its compounds *in vivo*

Test system	Test conditions	Substance (level of TCDD)	Result[1]	Comments	References
host-mediated assay	mouse, NMRI; 6 animals 2,4,5-T: 500 mg/kg body weight; intraperitoneal 2,4,5-T butyl ester: 1000 mg/kg body weight; intraperitoneal *S. typhimurium* G46 His^- *Serratia marcescens* a $21Leu^-$ examination of the peritoneal fluid after 3 hours	2,4,5-T; 2,4,5-T *n*-butyl ester (TCDD n.s.)	–		Buselmaier *et al*. 1972
dominant lethal test	mouse, NMRI; ♂ 100 mg/kg body weight; 1 × intraperitoneal groups of 1 ♂ with 3 ♀ mated during 6–8 weeks, examination after 12 days	2,4,5-T (TCDD n.s.)	–	no mutagenic effects	Buselmaier *et al*. 1972
dominant lethal test	rat, Chb:THOM; groups of 50 ♀ 0.1, 1, 10 mg/kg body weight; in the diet, 8 weeks groups of 2 ♀ with 1 ♂ mated during 1 week, examination after 12 days	2,4,5-T (50 ppb)	–	dose too low	Herbold *et al.* 1982
MNT[2], bone marrow, erythrocytes	mouse, CBA; groups of 3 ♂ 100 mg/kg body weight; 1 × intraperitoneal examination after 24 hours and 7 days	2,4,5-T (<1000 ppb)	–	slight toxic effects (fewer poly-chromatic erythrocytes)	Jenssen and Renberg 1976
CA[3], bone marrow	mouse, (Swiss × CBA) × Swiss; (DBA × CBA) × DBA; groups of 5 ♂ 2.5 mg/kg body weight; 1 × intraperitoneal examination after 6, 24, 48 hours 2.5 mg/kg body weight; 5 × intraperitoneal examination after 6 hours	2,4,5-T "pure" (TCDD n.s.)	–	dose too low	Dävring and Hultgren 1977
CA, bone marrow	mouse, (Swiss × CBA) × Swiss; (DBA × CBA) × DBA; groups of 5 ♂ 2.4, 60, 239 mg/kg body weight; 1 × intraperitoneal examination after 6, 24, 48 hours; 2.4, 60, 239 mg/kg body weight; 5 × intraperitoneal examination after 6 hours	2,4,5-T butoxyethyl ester herbicide (<100 ppb)	+	solvent and emulsifier alone also clastogenic	Dävring and Hultgren 1977

Table 8. continued

Test system	Test conditions	Substance (level of TCDD)	Result[1]	Comments	References
CA, spermato-gonia	Chinese hamster; groups of 13 ♂ 0.1, 1, 10, 100 mg/kg body weight; 5 × oral; examination after 24 hours	2,4,5-T (50 ppb)	–	from 10 mg/kg no significant increase in gaps and aberrations	Herbold *et al.* 1982
SLRL[4]	*D. melanogaster*/Karsnäs 60, ♂ 2 weeks, 1000 ppm, in the diet	2,4,5-T (<100 ppb)	+	effect very weak at high concentra-tions	Magnusson *et al*. 1977
SLRL	*D. melanogaster*/Oregon R, ♂ 15 days, 250, 1000 ppm, in the diet	2,4,5-T (not detectable)	+	positive after 1000 ppm	Majumdar and Golia 1974
SLRL	*D. melanogaster*/Berlin K, ♂ 3 days, 3.6, 7.2 mM, in the diet	2,4,5-T Na-salt (TCDD n.s.)	–	reduced fertility after 7.2 mM	Vogel and Chandler 1974
SLRL	*D. melanogaster*/Canton-SD, ♂ 72 hours, 1000, 10000 ppm, in the diet or a single injection of 10000 ppm	2,4,5-T, technical grade (TCDD n.s.)	–		Zimmering *et al*. 1985
non-disjunction, chromosome losses	*D. melanogaster*/yw^{a}f/yw^{a}f × ywaf/y^{+}YB^{S}, ♂+♀ whole larval period, 250 ppm, in the diet	2,4,5-T (TCDD n.s.)	–		Ramel and Magnusson 1979
non-disjunction, chromosome losses	D. melanogaster/yw^{a}f/yw^{a}f × ywaf/y^{+}Y B^{S}, ♂+♀ whole larval period, 250 ppm, in the diet	2,4,5-T butoxyethyl ester herbicide (<1000 ppb)	–		Magnusson *et al*. 1977
fertility/ embryo-genesis	*D. melanogaster*/Canton-S, ♂+♀ 5–6 days, 1, 50, 100, 250, 500 ppm, in the diet	2,4,5-T butoxyethyl ester herbicide (<100 ppb)	+	from 1 ppm effects on oogenesis	Dävring and Sunner 1971; Dävring 1975

[1] + positive, – negative
[2] micronucleus test
[3] chromosomal aberration
[4] test for X-chromosomal recessive lethal mutation
n.s. not specified

4.7 Carcinogenicity

4.7.1 Short-term studies

A group of 12 male Wistar rats were given a single intraperitoneal dose of diethylnitrosamine of 200 mg/kg body weight for initiation. After 2 weeks the animals were given 0.03 % 2-acetylaminofluorene in the diet for 2 weeks, during whicha single gavage dose of carbon tetrachloride of 2 ml/kg body weight was also administered after the first week. One week after the last dose of 2-acetylaminofluorene the animals were given 0.05 % 2,4,5-T (about 15 to 20 mg/kg body weight) as a promoter in the diet for 23 weeks. Liver tumours were observed in 2 of the 12 rats exposed to 2,4,5-T, but not in the 7 animals which only received the initiation treatment (Abdellatif *et al*. 1990). As the level of contamination of the 2,4,5-T samples with TCDD is not stated, it cannot be decided whether the observed effects were caused by 2,4,5-T or TCDD.

Groups of 15 female MRC-Wistar rats were given 2,4,5-T doses of 600 mg/kg feed (about 30 mg/kg body weight; 3.3 ppb TCDD) up to week 94 of life, either alone or in combination with 2-hydroxyethylnitrosourea (75 mg/l drinking water). 2,4,5-T alone had no influence on the formation of B cell lymphomas, nor did it influence the B cell-inducing effect of 2-hydroxyethylnitrosourea (Mirvish *et al*. 1991).

4.7.2 Long-term studies

In two long-term studies with rats (Celamerck 1979, Kociba *et al*. 1979) and one with two different strains of mice (Innes *et al*. 1969) no carcinogenic effects were found for 2,4,5-T (Table 9). In another study with mice (Muranyi-Kovacs *et al*. 1976) an increase was observed in the incidence of some rare tumours in one of the two mouse strains tested (Table 9). As in this study, however, only one dose was used, the number of animals used was small (22 males, 25 females) and there is no data for historical controls, it is unclear whether this is a substance-specific, dose-dependent effect or an incidental finding.

Table 9. Studies on the carcinogenicity of 2,4,5-T

Author:	Kociba *et al*. 1979
Substance:	2,4,5-T (purity 99 %); < 0.33 ppb TCDD
Species:	rat (Sprague-Dawley); groups of 50 ♂/♀
Administration:	in the diet
Dose:	3, 10, 30 mg/kg body weight
Duration:	2 years
Toxicity:	from 10 mg/kg body weight ♀: mineral deposits in kidneys, ♂: increase in coproporphyrin excretion 30 mg/kg body weight ♂+♀: decreased body weights, increased relative kidney weights, increase in amount of urine excreted, ♂: increase in urinary excretion of uroporphyrin
Tumours:	tumour incidence not increased

Table 9. continued

Author:	Celamerck 1979
Substance:	2,4,5-T (purity 99 %); 50 ppb TCDD
Species:	rat (Sprague-Dawley); groups of 50 ♂/♀
Administration:	*in utero*/lactation/in the diet
Dose:	3, 10, 30 mg/kg body weight
Duration:	30 months: exposure *in utero* and via lactation, from week 6 in the diet
Toxicity:	up to 30 mg/kg body weight no toxicologically relevant findings
Tumours:	tumour incidence not increased
Author:	Innes *et al.* 1969
Substance:	1) 2,4,5-T (purity not specified), 2) 2-(2,4,5-trichlorophenoxy)propionic acid, no data on TCDD concentration
Species:	mouse (F_1: C57BL/6xC3H/Anf and C57BL/6xAKR); groups of 18 ♂/♀
Administration:	days 7–28, gavage, then until 18th month in the diet
Dose:	1) about 21.5 mg/kg body weight (60 mg/kg in the diet) 2) about 46.4 mg/kg body weight (121 mg/kg in the diet)
Duration:	18 months
Toxicity:	no data
Tumours:	tumour incidence not increased
Author:	Muranyi-Kovacs *et al*. 1976
Substance:	2,4,5-T (purity not specified); < 50 ppb TCDD
Species:	mouse (C3Hf and XVII/G); groups of 19–25 ♂/♀
Administration:	the first two months via the drinking water, then in the diet
Dose:	100 mg/l drinking water, then 80 mg/kg feed, about 12 mg/kg body weight
Duration:	lifelong (average survival 516–632 days)
Toxicity:	not specified
Tumours:	XVII/G: ♂/♀: tumour incidence not increased C3Hf: ♂ (n = 22): 1 fibrosarcoma ♀ (n = 25): 1 osteosarcoma; 2 sarcomas; 2 cutaneous tumours, 1 cervical tumour

Sex	♂		♀	
mg/kg body weight	0	12	0	12
XVII/G				
number of animals	32	20	40	19
survival (days)	516	555	553	**632****
animals with tumours and/or leukemia (%)	78	75	53	84
"incidental" tumours (%)	78	70	48	84
lethal tumours (%)	–5	5	–	
C3Hf				
number of animals	43	22	44	25
survival (days)	641	**523****	661	**621***
animals with tumours and/or leukemia(%)	49	55	21	**48****
"incidental" tumours (%)	44	19	14	16
lethal tumours (%)	5**36****	7	**32****	

* $p < 0.1$, ** $p < 0.05$

5 Manifesto (MAK value, classification)

The available data from animal experiments on the carcinogenicity and genotoxicity of 2,4,5-T yielded no noteworthy positive results. The data indicate at most a weak clastogenic potential *in vitro*.

The NOEL for rats from long-term studies was given as 3 mg/kg body weight and for dogs as 2.4 mg/kg body weight. On the basis of a NOEL of 2.4 mg/kg body weight in the dog an exposure concentration without effect of 17 mg/m^3 can be calculated for a 70 kg person and an inhaled amount of air per workshift of 10 m^3. The current MAK value of 10 mg/m^3 is therefore regarded as adequate.

As 2,4,5-T is readily absorbed through the human skin the "H" designation has been retained.

The results of investigations of children whose mothers were exposed to 2,4,5-T during pregnancy can be accepted only with reservations; they do not indicate a marked increase in the occurrence of embryotoxic effects at the concentrations usually used. The available somewhat unsatisfactory studies involving uptake of presumably high doses of 2,4,5-T or 2,4,5-T highly contaminated with TCDD do not allow the exclusion of embryotoxic effects. The available studies are, however, not appropriate for the evaluation of potential toxic effects of 2,4,5-T on reproduction in man. The results of numerous studies with various species of animal have therefore been used. Mice were found to be the most sensitive species with an effect threshold between 15 and 40 mg/kg body weight. In rats, hamsters, rabbits and in particular in monkeys, the species most readily compared with man, there was a consistent effect threshold for 2,4,5-T of 40 to 50 mg/kg body weight. This effect threshold is sufficiently far from the MAK value, which corresponds to a dose of about 1.5 mg/kg body weight. Therefore 2,4,5-T and its salts and esters are classified in Pregnancy risk group C.

6 References

Abdellatif AG, Préat V, Vamecq J, Nilsson R, Roberfroid M (1990) Peroxisome proliferation and modulation of rat liver carcinogenesis by 2,4-dichlorophenoxyacetic acid, 2,4,5-trichlorophenoxyacetic acid, perfluorooctanoic acid and nafenopin. *Carcinogenesis 11*: 1899–1902

Anderson D, Styles JA (1978) The bacterial mutation test. *Br J Cancer 37*: 924–930

Asp S, Riihimäki V, Hernberg S, Pukkala E (1994) Mortality and cancer morbidity of Finnish chlorophenoxy herbicide applicators: an 18-year prospective follow-up. *Am J Ind Med 26*: 243–253

Båge G, Cekanova E, Larsson KS (1973) Teratogenic and embryotoxic effects of the herbicides di- and trichlorophenoxyacetic acid (2,4-D and 2,4,5–T). *Acta Pharmacol Toxicol 32*: 408–416

Beck SL (1981) Assessment of adult skeletons to detect prenatal exposure to 2,4,5-T or Trifluralin in mice. *Teratology 23*: 33–55

Beraterforum für Präventivmedizin und Umweltschutz (1977) *Subchronische toxikologische Untersuchungen an Hunden (Fütterungsversuch über 3 Monate)*. Prof Dr med U Mohr, unpublished investigation by the Beraterforum für Präventivmedizin und Umweltschutz GmbH, Hamburg

Boehringer (1970a) *Prüfung der Substanz 2,4,5-T auf Teratogenität an Ratten*. Unpublished investigation by CH Boehringer Sohn, Ingelheim am Rhein, 10. Dezember 1970

Boehringer (1970b) *Subakute Toxizitätsprüfung der Substanz 2,4,5-T-Mischbutylester an Ratten bei oraler Applikation*. Unpublished investigation by CH Boehringer Sohn, Ingelheim am Rhein. cited in: DFG (1982), [54]

Boehringer (1971) *Prüfung der Substanz 2,4,5-T auf Teratogenität an Ratten (Technische Charge 70 200/371)*. Unpublished investigation by CH Boehringer Sohn, Ingelheim am Rhein, 18th June 1971

Buselmaier W, Röhrborn G, Propping P (1972) Mutagenitäts-Untersuchungen mit Pestiziden im Host-mediated assay und mit dem Dominanten Letaltest an der Maus. *Biol Zentralbl 91*: 311–325

Celamerck (1974a) *Hormoslyr 500-T: Prüfung auf teratogene Wirkung an Mäusen nach Inhalation*. Merck Report No. 4/56/74, unpublished investigation by Celamerck GmbH u. Co KG, Ingelheim am Rhein

Celamerck (1974b) *Hormoslyr 500-T: Prüfung auf teratogene Wirkung an Mäusen nach oraler Applikation*. Merck Report No. 4/29/74, unpublished investigation by Celamerck GmbH u. Co KG, Ingelheim am Rhein

Celamerck (1974c) *Hormoslyr 500-T: Prüfung auf teratogene Wirkung an Mäusen nach oraler Applikation. Ergänzende Untersuchung zu unseren früheren Prüfungen*. Merck Report No. 4/30/74, unpublished investigation by Celamerck GmbH u. Co KG, Ingelheim am Rhein

Celamerck (1974d) *Tormona Salz: Prüfung auf teratogene Wirkung an Mäusen nach oraler Applikation*. Merck Report No. 4/100/74, unpublished investigation by Celamerck GmbH u. Co KG, Ingelheim am Rhein

Celamerck (1975a) *2,4,5-Trichlorphenoxyessigsäure-Diäthylaminsalz: Prüfung auf teratogene Wirkung an Mäusen nach oraler Applikation*. Merck Report No. 4/11/75, Unpublished investigation by Celamerck GmbH u. Co KG, Ingelheim am Rhein

Celamerck (1975b) *2,4,5-Trichlorphenoxyessigsäure-Diäthylaminsalz: Prüfung auf teratogene Wirkung an Mäusen nach Inhalation*. Merck Report No. 4/33/75, unpublished investigation by Celamerck GmbH u. Co KG, Ingelheim am Rhein

Celamerck (1978) *Chronic oral toxicity of 2,4,5-T, batch no 503, control no 153574 B—short "2,4,5-T"—in a reproduction study covering three generations of Sprague-Dawley rats*. Laboratorium für Pharmakologie und Toxikologie Prof Dr F Leuschner, unpublished investigation by Celamerck GmbH u. Co KG, Ingelheim am Rhein

Celamerck (1979) *Chronic oral toxicity of 2,4,5-T, batch no 503, control no 153574 B—called for short "2,4,5-T"—in Sprague-Dawley (SIV 50) rats*. Laboratorium für Pharmakologie und Toxikologie Prof. Dr. F. Leuschner, unpublished investigation by Celamerck GmbH u. Co KG, Ingelheim am Rhein

Collins TFX, Williams CH (1971) Teratogenic studies with 2,4,5-T and 2,4-D in the hamster. *Bull Environ Contam Toxicol 6*: 559–567

Courtney KD (1977) Prenatal effects of herbicides: evaluation by the prenatal development index. *Arch Environ Contam Toxicol 6*: 33–46

Courtney KD, Moore JA (1971) Teratology studies with 2,4,5-trichlorophenoxyacetic acid and 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Toxicol Appl Pharmacol 20*: 396–403

Courtney KD, Gaylor DW, Hogan MD, Falk HL, Bates RR, Mitchell I (1970) Teratogenic evaluation of 2,4,5-T. *Science 168*: 864–866

Dävring L (1975) Effects of a 2,4,5-T ester on early oogenesis, fertility and development in Drosophila melanogaster. *Hereditas 80*: 255–262

Dävring L, Sunner M (1971) Cytogenetic effects of 2,4,5-trichlorophenoxyacetic acid on oogenesis and early embryogenesis in Drosophila melanogaster. *Hereditas 68*: 115–122

Dävring L, Hultgren K (1977) Cytogenetic effects on in vivo bone-marrow cells of Mus musculus induced by a commercial 2,4,5-T ester product. *Hereditas 85*: 123–134

DFG (Deutsche Forschungsgemeinschaft) (1982) *Datensammlung zur Toxikologie der Herbizide: 2,4,5-T*. Arbeitsgruppe Toxikologie der Kommission für Pflanzenschutz-, Pflanzenbehandlungs- und Vorratsschutzmittel, VCH, Weinheim

Donovan JW, MacLennan R, Adena M (1984) Vietnam service and the risk of congenital anomalies. *Med J Aust 140*: 394–397

Dougherty WJ, Herbst M, Coulston F (1975) The non-teratogenicity of 2,4,5-trichlorophenoxyacetic acid in the Rhesus monkey (Macaca mulatta). *Bull Environ Contam Toxicol 13*: 447–482

DOW (1961) *Results of 90-day feeding studies on Dowanol 97B (mono-, di- and tripropylene glycol butyl ether) esters of 2,4,5-T in rats*. Unpublished investigation by the DOW Chemical Company. cited in: FAO/WHO (1976)

DOW (1970) *A 90-day dietary feeding study on 2,4,5-trichlorophenoxyacetic acid in rats*. Unpublished investigation by the DOW Chemical Company. cited in: FAO/WHO (1976)

Drill VA, Hiratzka T (1953) Toxicity of 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid. *Ind Hyg Occup Med 7*: 61–67

Emerson JL, Thompson DJ, Strebing RJ, Gerbig CG, Robinson VB (1971) Teratogenic studies on 2,4,5-trichlorophenoxyacetic acid in the rat and rabbit. *Food Cosmet Toxicol 9*: 395–404

Erickson JD, Mulinare J, McClain PW, Fitch TG, James LM, McClearn AB, Adams MJ (1984) Vietnam veterans' risk for fathering babies with birth defects. *J Am Med Assoc 252*: 903–912

Fang SC, Lindstrom FT (1980) In vitro binding of ^{14}C-labeled acidic compounds to serum albumin and their tissue distribution in the rat. *J Pharmacokinet Biopharm 8*: 583–591

Fang SC, Fallin E, Montgomery ML, Freed VH (1973) Metabolism and distribution of 2,4,5-trichlorophenoxyacetic acid in female rats. *Toxicol Appl Pharmacol 24*: 555–563

FAO/WHO (1976) *2,4,5-T, 1970 evaluations of some pesticide residues in food*. Food and Agriculture Organization of the United Nations plant production and protection, 459–477

Field B, Kerr C (1979) Herbicide use and incidence of neural-tube defects. *Lancet 1*: 1341–1342

Galloway SM, Armstrong MJ, Reuben C, Colman S, Brown B, Cannon C, Bloom AD, Nakamura F, Ahmed M, Duk S, Rimpo J, Margolin BH, Resnick MA, Anderson B, Zeiger E (1987) Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: evaluation of 108 chemicals. *Environ Mol Mutagen 10, Suppl 10*: 1–175

Gehring PJ, Kramer CG, Schwetz BA, Rose JQ, Rowe VK (1973) The fate of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) following oral administration to man. *Toxicol Appl Pharmacol 26*: 352–361

George SE, Whitehouse DA, Claxton LD (1992) Genotoxicity of 2,4,5-trichlorophenoxyacetic acid biodegradation products in the Salmonella reversion and lambda prophage-induction bioassay. *Environ Toxicol Chem 11*: 733–740

Greim H (Ed.) (1993) *Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werten*, 19th issue, 2,3,7,8-Tetrachlordibenzo-p-dioxin, VCH-Verlagsgesellschaft, Weinheim

Grunow W, Böhme C (1974) Über den Stoffwechsel von 2,4,5-T und 2,4-D bei Ratten und Mäusen. *Arch Toxicol 32*: 217–225

Hanif JA, Metcalf P, Nobbs CL, Worsley KJ (1981) Aerial spraying of 2,4,5-T and human birth malformations: an epidemiological investigation. *Science 212*: 249–351

Herbold BA, Machemer L, Röhrborn G (1982) Mutagenicity studies with 2,4,5-T on bacteria and mammalian germ cells. *Teratogen Carcinogen Mutagen 2*: 91–101

Highman B, Gaines TB, Schumacher HJ, Haley TJ (1976a) Strain differences in histopathologic, hematologic, and blood chemistry changes induced in mice by technical and purified preparation of 2,4,5-trichlorophenoxyacetic acid. *J Toxicol Environ Health 1*: 1041–1054

Highman B, Gaines TB, Schumacher HJ (1976b) Sequential histopathologic, hematologic, and blood chemistry changes induced in mice by a technical and a purified preparation of 2,4,5-trichlorophenoxyacetic acid. *J Toxicol Environ Health 1*: 469–484

Holson JF, Gaines TB, Nelson CJ, LaBorde JB, Gaylor DW, Sheehan DM, Young JF (1992) Developmental toxicity of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). I. Multireplicated dose-response studies in four inbred and one outbred stock of mice. *Fundam Appl Toxicol 19*: 286–297

Hood RD, Patterson BL, Thacker GT, Sloan GL, Szczech GM (1979) Prenatal effects of 2,4,5-T, 2,4,5-trichlorophenol and phenoxyacetic acid in mice. *J Environ Sci Health C 13*: 189–204

Hook JB, Cardona R, Osborn JL, Bailie MD (1976) The renal handling of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) in the dog. *Food Cosmet Toxicol 14*: 19–23

Innes JRM, Ulland BM, Valerio MG, Petrucelli L, Fishbein L, Hart ER, Pallotta AJ, Bates RR, Falk HL, Gart JJ, Klein M, Mitchell I, Peters J (1969) Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: a preliminary note. *J Nat Cancer Inst 42*: 1101–1114

Jenssen D, Renberg L (1976) Distribution and cytogenetic test of 2,4-D and 2,4,5-T phenoxyacetic acids in mouse blood tissue. *Chem Biol Interact 14*: 291–299

Khera KS, McKinley WP (1972) Pre- and postnatal studies on 2,4,5-trichlorophenoxyacetic acid, 2,4-dichlorophenoxyacetic acid and their derivatives in rats. *Toxicol Appl Pharmacol 22*: 14–28

Kociba RJ, Keyes DG, Lisowe RW, Kalmins RP, Dittenberger DD, Wade CE, Gorzinsky SJ, Mahle NH, Schwetz BA (1979) Results of a two-year chronic toxicity and oncogenic study of rats ingesting diets containing 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). *Food Cosmet Toxicol 17*: 205–221

Koschier FJ, Berndt WO (1977) Evaluation of acute and short-term administration of 2,4,5-trichlorophenoxyacetate with respect to renal proximal tubular transport. *Food Cosmet Toxicol 15*: 297–301

Leuschner (1980) *13 weeks toxicity of 2,4,5-T, batch no 503 (Chemie Linz, AG Code No 153574b) in beagle dogs after administration in the food*. Unpublished report. cited in: DFG (1982), [248]

Magnusson I, Ramel C, Eriksson A (1977) Mutagenic effects of chlorinated phenoxyacetic acids in Drosophila melanogaster. *Hereditas 87*: 121–123

Majumdar SK, Golia JK (1974) Mutation test of 2,4,5-trichlorophenoxyacetic acid on Drosophila melanogaster. *Can J Genet Cytol 16*: 465–466

Matsuoka A, Sawada M, Sofuni T, Ishidate Jr M (1988) Chromosome aberration test on 25 chemicals – Cooperative study with NTP of USA. *Mutat Res 203*: 377–378

Merck (1972a) *2,4,5-T: Prüfung auf teratogene Wirkung an Mäusen bei oraler Applikation*. Report No. 4/189/72, unpublished

Merck (1972b) *2,4,5-T: Prüfung auf teratogene Wirkung an Mäusen bei oraler Applikation*. Report No. 4/190/72, unpublished

Mersch-Sundermann V, Dickgiesser N, Hablizel U, Gruber B (1988) Untersuchungen zur Mutagenität organischer Mikrokontaminationen in der Umwelt. I. Mitteilung: Die Mutagenität ausgewählter Herbizide und Insektizide im Salmonella-Mikrosomen-Test (Ames-Test) unter Berücksichtigung der pathogenen Potenz kontaminierter Grundwässer. *Zentralbl Bakteriol Hyg B 186*: 247–260

Mersch-Sundermann V, Hofmeister A, Müller G, Hof H (1989) Untersuchung zur Mutagenität organischer Mikrokontaminationen in der Umwelt. III. Mitteilung: Die Mutagenität ausgewählter Herbizide und Insektizide im SOS-Chromotest. *Zentralbl Hyg 189*: 135–146

Mirvish SS, Nickols J, Weisenburger DD, Johnson D, Joshi SS, Kaplan P, Gross M, Tong HY (1991) Effects of 2,4,5-trichlorophenoxyacetic acid, pentachlorophenol, methylprednisolone, and Freund's adjuvant on 2-hydroxyethylnitrosourea carcinogenesis in MRC-Wistar rats. *J Toxicol Environ Health 32*: 59–74

Mortelmans K, Haworth S, Speck W, Zeiger E (1984) Mutagenicity testing of Agent Orange components and related chemicals. *Toxicol Appl Pharmacol 75*: 137–146

Muranyi-Kovacs I, Rudali G, Imbert J (1976) Bioassay of 2,4,5-trichlorophenoxyacetic acid for carcinogenicity in mice. *Br J Cancer 33*: 626–633

Murray FJ, Smith FA, Nitschke KD, Humiston CG, Kociba RJ, Schwetz BA (1979) Three-generation study of rats given 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in the diet. *Toxicol Appl Pharmacol 50*: 241–252

Nelson CJ, Holson JF, Green HG, Gaylor DW (1979) Retrospective study of the relationship between agricultural use of 2,4,5-T and cleft palate occurence in Arkansas. *Teratology 19*: 377–384

Neubert D, Dillmann I (1972) Embryotoxic effects in mice treated with 2,4,5-trichlorophenoxyacetic acid and 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Naunyn-Schmiedeberg's Arch Pharmacol 272*: 243–264

Parschu GL, Dunn FL, Rowe VK (1971a) Study of the teratogenicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in the rat. *Food Cosmet Toxicol 9*: 405–412

Parschu GL, Dunn FL, Lisowe RW, Rowe VK (1971b) Study of the effect of high levels of 2,4,5-trichlorophenoxyacetic acid on foetal development in the rat. *Food Cosmet Toxicol 9*: 527–530

Phuong NTN, Thuy TT, Phuong PK (1989) An estimate of reproductive abnormalities in women inhabiting herbicide sprayed and non-herbicide sprayed areas in the south of Vietnam, 1952–1981. *Chemosphere 18*: 843–846

Piper WN, Rose JQ, Leng ML, Gehring PJ (1973) The fate of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) following oral administration to rats and dogs. *Toxicol Appl Pharmacol 26*: 339–351

Ramel C, Magnusson J (1979) Chemical induction of nondisjunction in Drosophila. *Environ Health Perspect 31*: 59–66

Rashid KA, Mumma RO (1986) Screening pesticides for their ability to damage bacterial DNA. *J Environ Sci Health B21*: 319–334

Roll R (1971) Untersuchungen über die teratogene Wirkung von 2,4,5-T bei Mäusen. *Food Cosmet Toxicol 9*: 671–676

Rubinstein C, Jone C, Trosko JE, Chang C-C (1984) Inhibition of intercellular communication in cultures of chinese hamster V79 cells by 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid. *Fundam Appl Toxicol 4*: 731–739

Sare WM, Forbes PI (1972) Possible dysmorphogenic effects of an agricultural chemical: 2,4,5-T. *N Z Med J 75*: 37–38

Seiler JP (1979) Phenoxyacids as inhibitors of testicular DNA synthesis in male mice. *Bull Environ Contam Toxicol 21*: 89–92

Shirasu Y, Moriya M, Kato K, Furuhashi A, Kada T (1976) Mutagenicity screening of pesticides in the microbial system. *Mutat Res 40*: 19–30

Siebert D, Lemperle E (1974) Genetic effects of herbicides. Induction of mitotic gene conversion in Saccharomyces cerevisiae. *Mutat Res 22*: 111–120

Smith FA, Schwetz BA, Nitschke KD (1976) Teratogenicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in CF-1 mice. *Toxicol Appl Pharmacol 38*: 517–523

Smith FA, Murray FJ, John JA, Nitschke KD, Kociba RJ, Schwetz BA (1981a) Three-generation reproduction study of rats ingesting 2,4,5-trichlorophenoxyacetic acid in the diet. *Food Cosmet Toxicol 19*: 41–45

Smith AH, Matheson DP, Fisher DO, Chapman CJ (1981b) Preliminary report of reproductive outcomes among pesticide applicators using 2,4,5-T. *N Z Med J 93*: 177–179

Smith AH, Fisher DO, Pearce N, Chapman CJ (1982) Congenital defects and miscarriages among New Zealand 2,4,5-T sprayers. *Arch Environ Health 37*: 197–200

Thomas (1980) 2,4,5-T use and congenital malformation rates in Hungary. *Lancet 2*: 214–215

Thompson DJ, Emerson JL, Parschu GL (1971) Study of the effects of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) on rat and rabbit fetal development. *Teratology 4*: 243

Townsend JC, Bodner KM, Van Peenen PFD, Olson RD, Cook RR (1982) Survey of reproductive events of wives of employees exposed to chlorinated dioxins. *Am J Epidemiol 115*: 695–713

Tyynelä K, Elo HA, Ylitalo P (1990) Distribution of three common chlorophenoxyacetic acid herbicides into the rat brain. *Arch Toxicol 64*: 61–65

Vogel E, Chandler JLR (1974) Mutagenicity testing of cyclamate and some pesticides in Drosophila melanogaster. *Experientia 36*: 621–623

White FMM, Cohen FG, Sherman G, McCurdy R (1988) Chemicals, birth defects and stillbirths in New Brunswick: associations with agricultural activity. *Can Med Assoc J 138*: 117–124

Wilson JG (1971) *Report on the treatment of pregnant Rhesus monkeys with 2,4,5-T acid*. Unpublished investigation by the Children's Hospital Research Foundation and Department of Pediatrics and Anatomy, University of Cincinnati, College of Medicine, Cincinnati, Ohio

Zhao Y, Li W, Chou I-N (1987) Cytoskeletal perturbation induced by herbicides, 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). *J Toxicol Environ Health 20*: 11–26

Zetterberg G (1978) Genetic effects of phenoxy acids on microorganisms. In: Ramel C (Ed) Chlorinated phenoxy acids and their dioxins. *Ecol Bull 27*: 193–204

Zimmering S, Mason JM, Valencia R, Woodruff RC (1985) Chemical mutagenesis testing in Drosophila. II. Results of 20 coded compounds tested for the National Toxicology Program. *Environ Mutagen 7*: 87–100

completed 23.03.1995