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Chronic Oral Toxicity of 2,4,5-T  
Batch No. 503 in a Reproduction Study Covering Three Generations of Sprague-Dawley Rats.  
Author: Celamerck, GmbH & Co. K.G. at Laboratorium Fur Pharmakologie und Toxikologie, dated May 2, 1978.

A three generation reproduction study was carried out using 20/sex of the 2nd litter in each generation of P, F and F<sub>2</sub> to produce the succeeding generations. A group of 20/sex untreated were controls. Dosages of 0, 3, 10 and 30 mg/kg were used. The animals P parents were 39 - 42 days for males and females respectively at the start.

(TCDD 2,3,7,8-tetrachloro-dibenzo-p-dioxin was stated to be 0.05 ppm.

A pretreatment period prior to breeding tests was given

P generation	8 and 16 weeks
F <sub>1</sub>	15 and 24 weeks
F <sub>2</sub>	15 and 24 weeks

Matings were monogramous for a period of 1 week. If mating was negative, partners were changed every seven days.

The sensitivity of fetuses and pups was examined by sacrifice of the dams after weaning of the 2nd litters for the evidence of implantations lost.

The pups not used as parents for the next generation were sacrificed and inspected for external and internal malformations.

#### Results:

1. Wt. changes from those of controls were not observed in any dose level used.
2. Fertility examinations of the P, F<sub>1</sub> and F<sub>2</sub> generations were similar in all groups in the study to include the:
  - a. duration of pregnancy
  - b. number of pups alive and dead and numbers of implantation sites
  - c. numbers of pups per dam
  - d. sex of pups
  - e. stillborns
3. A behavior study and sensory examination was completed which was considered normal.

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Wt. Changes pups of 20/sex/generation

Generation	Control		3 mg/kg		10 mg/kg		30 mg/kg	
	M	F	M	F	M	F	M	F
P	102.4	101.8	101.8	101.7	102.2	101.9	102.2	102
F <sub>1</sub>	64.6	62	66	61.6	65.9	61.8	65.2	60.1
F <sub>2</sub>	66.4	63.2	67.2	62.7	65.8	63.4	68.4	60.6
F <sub>3</sub>	66.3	61.4	66.4	62.1	67.8	60.4	67.7	62

Fertility: mean number of copulations required

Generation	Litter							
	Control		3 mg		10 mg		30 mg	
	1	2	1	2	1	2	1	2
P	5.8	6.3	5.0	5.8	4.7	3.3	5.0	3.6
F <sub>1</sub>	2.8	5.5	3.2	4.9	3.8	3.4	3.3	3.7
F <sub>2</sub>	3.8	4.6	4.9	5.2	5.9	3.7	3.7	3.9

Length of pregnancy varied from 21 to 22 days in all generations.

The numbers of pups alive at birth per dam were not similar in all groups.

Generation/Litter	Controls	3 mg/kg	10 mg/kg	30 mg/kg
P <sub>1</sub>	11.9	11.7	11.4	11.9
P <sub>2</sub>	11.2	11.3	12.2	12.7
F <sub>1</sub> 1	11.8	12.0	12.6	11.8
F <sub>1</sub> 2	12.2	11.7	11.7	11.7
F <sub>2</sub> 1	11.4	11.2	12.4	12.4
F <sub>2</sub> 2	11.4	11.7	11.7	11.5

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Malformed pups were noted only -- Absolute Numbers

Generation/Litter	Controls	3 mg/kg	10 mg/kg	30 mg/kg
P <sub>1</sub>	--	--	1	--
P <sub>2</sub>	--	--	--	1 runt
F <sub>1</sub> 1	--	--	--	--
F <sub>1</sub> 2	--	--	--	--
F <sub>2</sub> 1	1 runt	--	--	--
F <sub>2</sub> 2	--	--	1 runt 1 still.	--

Pup body weights at birth and after 3 weeks did not differ statistically from controls. Viability at the 3rd week was essentially the same as controls.

The test of sensory functions showed no changes in reflexes, muscle tone, coordination, consciousness, emotional behavior, activity and reactivity and central excitation in any generation (litters 1 and 2) and dose levels from controls.

This study showed no sensitivity of fetuses in utero to the test doses when the number of implantations and viable fetuses were counted in the dams of the 2nd litters of each generation.

	Fetuses	Implants loss/fetuses	Dams w/implant loss
P/control	201	19/201	11/18
P/3 mg	192	20/192	9/17
P/10 mg	243	17/243	7/20
P 30/mg	241	16/241	7/19
F <sub>1</sub> /control	207	13/207	6/17
F <sub>1</sub> /3 mg	211	?/211 <u>errors</u>	10/18 ?
F <sub>1</sub> /10 mg	233	25/233	12/20
F <sub>1</sub> /30 mg	223	23/223	11/19
F <sub>2</sub> /control	205	19/205	10/18
F <sub>2</sub> /3 mg	199	13/199	8/17
F <sub>2</sub> /10 mg	223	11/223	6/19
F <sub>2</sub> /30 mg	218	17/218	9/19

Microscopic examination of the pups of the F<sub>3</sub> generation suggests a microscopic effect of hepatocellular swelling and fatty degeneration at 30 mg/kg in the young rats after in utero, lactation and six weeks on food after weaning.

This reviewer classifies the study as CORE minimum data and the NOEL would be considered to be 30 mg/kg for reproductive effects.

However, the NOEL for the study on the pups must be conservatively considered to be 10 mg/kg since the study does not delineate whether the effects suggested in the female livers were from in utero and lactation effects or the additional six weeks of feeding.