NTP
National Toxicology Program

Tris(chloropropyl) phosphate (TCPP)

NTP Technical Report on the Prenatal Developmental Toxicity Studies of Tris(chloropropyl) phosphate in Sprague Dawley (Hsd:Sprague Dawley SD) Rats (Gavage Studies)

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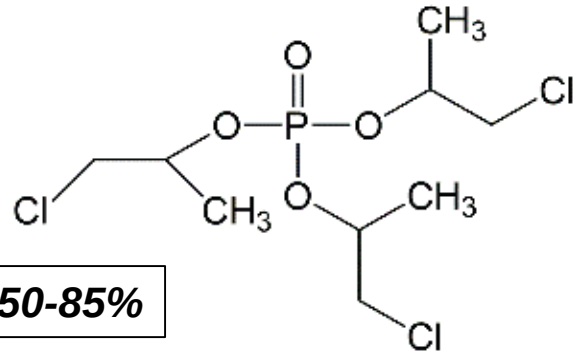
Peer-Review Meeting
July 31, 2019

Tris(chloropropyl) phosphate (TCPP)

- Flame retardant in a variety of commercial and consumer products
  - Flexible polyurethane foam used in home furnishings or construction materials, textile waterproofing spray, electronics, etc
- Ubiquitous, but not bioaccumulative, in the environment
  - Detected in drinking, ground, and surface waters, sediment, household dust, indoor air, and marine food sources (e.g., fish, mussels, etc)
- Exposure can occur from dermal, oral or inhalation routes
  - Measured in human plasma, breast milk, and urine
  - Occupational exposures detected by air sampling, hand wipes, and urine

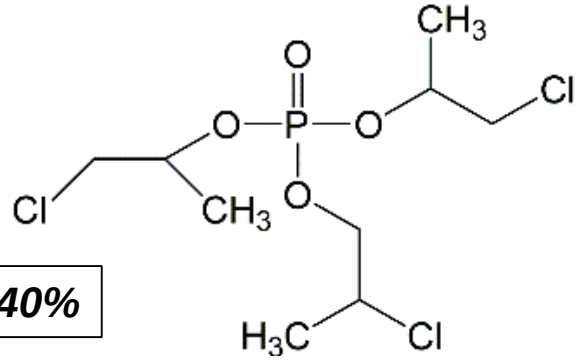
Background

Tris(1-chloro-2-propyl) phosphate



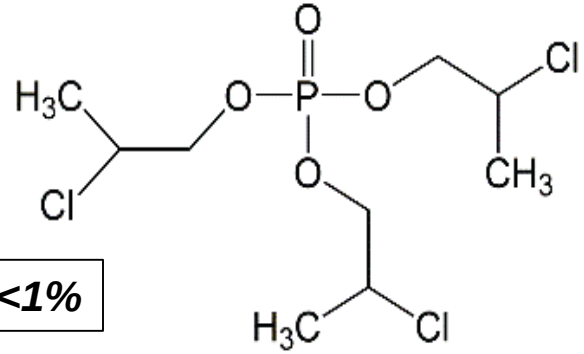
50-85%

Bis(2-chloro-1-methylethyl) 2-chloropropyl phosphate



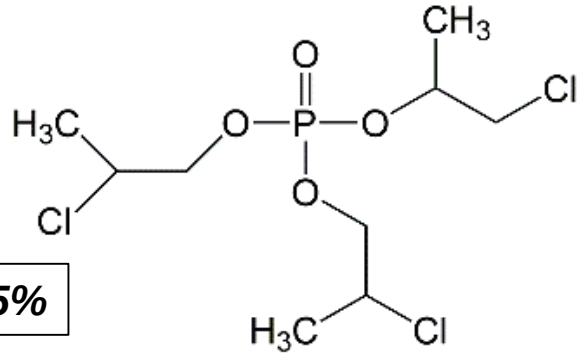
15-40%

Tris(2-chloropropyl) phosphate



<1%

Bis(2-chloropropyl) 2-chloroisopropyl phosphate



<15%

Background

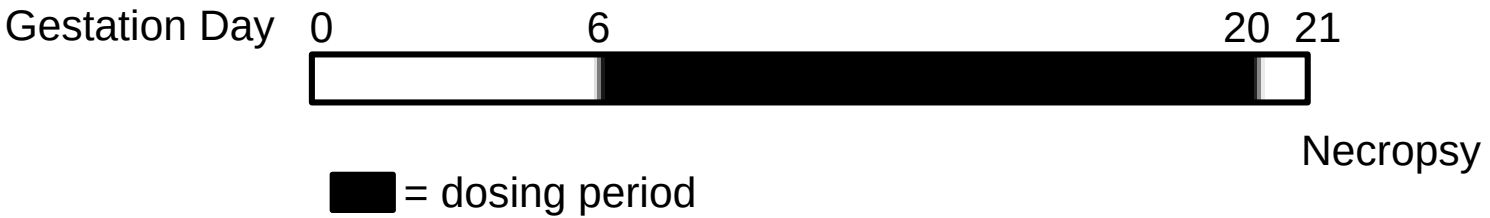
- Reports indicating that TCPP exposure to consumers is expected to increase due to the phasing out of other classes of flame retardants

- Insufficient toxicity data to assess potential health risks, *including developmental toxicity from in utero exposure*

Study Goal

Characterize the effects of oral TCPP administration in pregnant rats and on fetal development

Dose Range-Finding Study Design



- **Doses: 0, 300, 650, 1000 mg/kg/day (gavage)**
- N=11 time-mated, female rats per group
- Maternal endpoints: Clinical observations, body weights, feed consumption, and uterine parameters
- Fetal endpoints: Fetal weight, external examination, and litter parameters including number of live/dead fetuses, and sex ratio

Dose Range-Finding Study: Maternal Findings

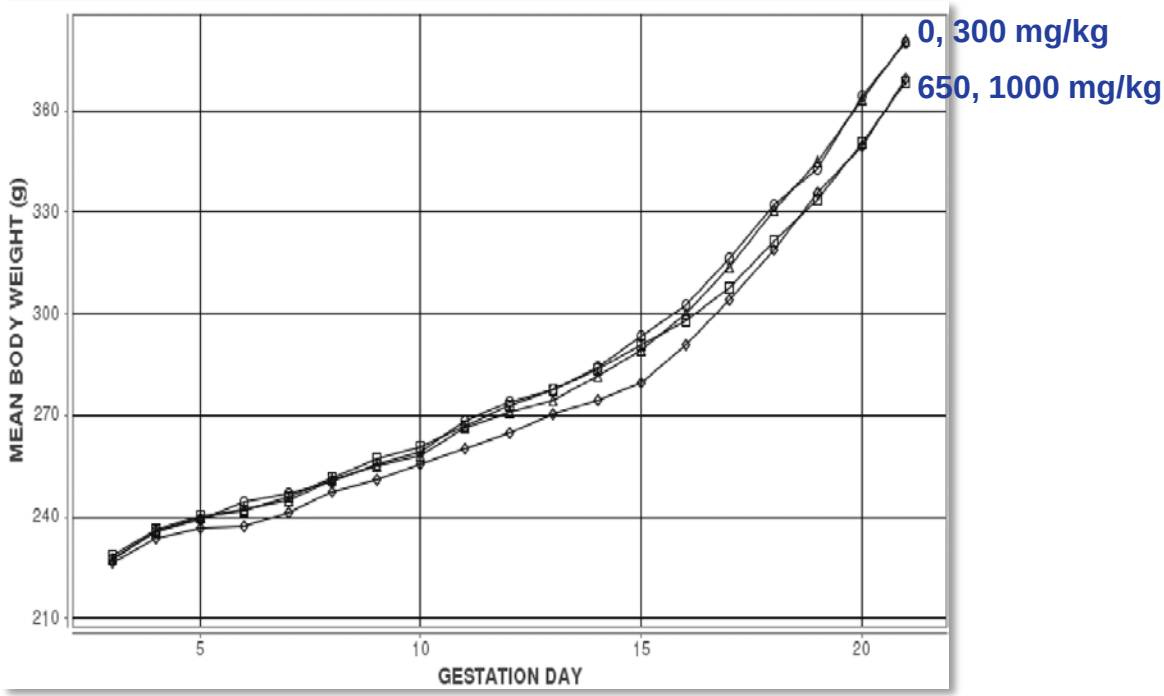
- Toxicity observed in the 1,000 mg/kg group: 7 of 11 dams found dead or euthanized moribund
  - Spectrum of clinical signs (majority as single day occurrence) observed throughout gestation
    - convulsions, tremors, and hypoactivity, gasping, hunched posture, nasal discharge, stained fur, piloerection, prone, salivation, and rooting

- One female in the 650 mg/kg group was euthanized moribund on gestation day 16 with associated clinical observations similar to the 1000 mg/kg group

- No toxicity observed at 300 mg/kg

Dose Range-Finding Study: Maternal Findings

- No treatment-related effects on
  - Maternal absolute body weights at GD21
  - Maternal body weight gain from GD6-21



Dose Range-Finding Study: Uterine and Litter Parameters

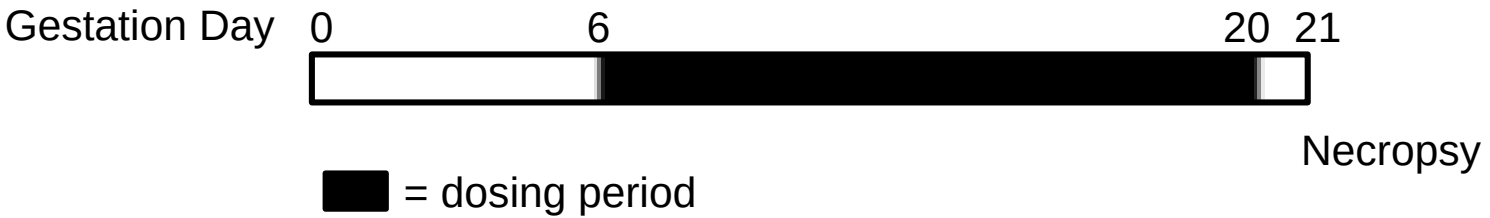
Endpoint	0 mg/kg	300 mg/kg	650 mg/kg	1000 mg/kg
Maternal Terminal Body Weight (g)	378.7 ± 5.7	376.4 ± 6.3	363.9 ± 20.4	365.0 ± 10.1
Gravid Uterine Weight (g)	98.1 ± 4.0	96.6 ± 3.4	86.4 ± 9.8	74.7 ± 16.0
No. Litters	10	11	7	4
No. Live Fetuses	136	147	83	42
No. Live Fetuses per Litter	13.6 ± 0.7	13.4 ± 0.6	11.9 ± 1.4	10.5 ± 2.5
No. Resorptions (Early + Late)	3	1	2	1
No. Whole Litter Resorptions	0	0	0	0
Post-implantation Loss	2.1 ± 2.1%	0.8 ± 0.8%	6.5 ± 4.0%	1.9 ± 1.9%
Fetal Weight per Litter (g)	5.13 ± 0.06	5.24 ± 0.09	5.20 ± 0.10	5.23 ± 0.22

Values are reported as counts or mean ± standard error; (g) = grams

- Appearance of a dose-related findings

  ⇨ However there was a low number of litters available to fully characterize embryo-fetal toxicity or growth retardation

Main Study Design

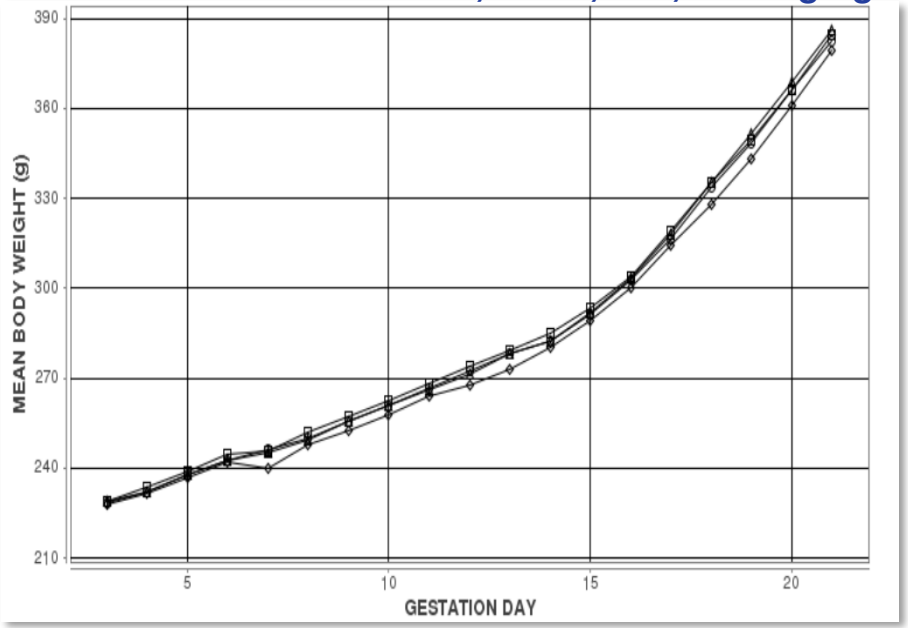


- **Doses: 0, 162.5, 325, 650 mg/kg/day (gavage)**
- N=25 time-mated, female rats per group
  - Additional animals (N=25) were added to the vehicle control group to obtain historical control data for both maternal and fetal findings in this strain of rat
- Endpoints (in addition to those assessed in the Dose Range-Finding study):
  - Maternal: Organ weight measurements including ovary, liver, and adrenal glands
  - Fetal: Visceral, head, and skeletal examinations

Main Study: Maternal Findings

- No dams were removed due to morbidity or mortality
- Clinical observations at 650 mg/kg
  - Low incidences of nasal discharge, salivation, twitches, ataxia, hyperactivity, etc
- No treatment-related effects on
  - Maternal absolute body weights at GD21
  - Maternal body weight gain from GD6-21

0, 162.5, 325, 650 mg/kg



Main Study: Maternal Findings

Endpoint	0 mg/kg	162.5 mg/kg	325 mg/kg	650 mg/kg
Maternal Terminal Body Weight (g)	378.5 ± 3.0	382.7 ± 4.0	383.1 ± 5.2	375.2 ± 8.3
Liver				
Absolute (g)	14.25 ± 0.19**	15.62 ± 0.32**	16.58 ± 0.27**	18.02 ± 0.56**
Relative	37.93 ± 0.41**	40.78 ± 0.67**	43.39 ± 0.78**	48.09 ± 1.09**

** Statistically significant (P≤0.01) trend (by Jonckheere's test) or pairwise comparison (by Williams' or Dunnett's test)
g =grams; liver-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight
Data are displayed as mean ± standard error

- Observed treatment-related increases:
  - Absolute liver weights
  - Relative liver weights

- No treatment-related effects on ovary or adrenal gland weights

Main Study: Uterine and Litter Parameters

Endpoint	0 mg/kg	162.5 mg/kg	325 mg/kg	650 mg/kg
Maternal Terminal Body Weight (g)	378.5 ± 3.0	382.7 ± 4.0	383.1 ± 5.2	375.2 ± 8.3
Gravid Uterine Weight (g)	98.9 ± 1.9	102.0 ± 2.2	95.8 ± 4.1	91.8 ± 5.9
No. Litters	44	21	21	20
No. Live Fetuses	599	300	270	259
No. Live Fetuses per Litter	13.6 ± 0.3	14.3 ± 0.4	12.9 ± 0.6	12.9 ± 0.9
No. Resorptions (Early + Late)	24	11	11	15
No. Whole Litter Resorptions	0	0	0	0
Post-implantation Loss	3.8 ± 1.1%	3.4 ± 1.0%	4.3 ± 1.2 %	7.2 ± 4.5%
Fetal Weight per Litter (g)	5.29 ± 0.04	5.22 ± 0.06	5.42 ± 0.08	5.22 ± 0.07

Values are reported as counts or mean ± standard error; (g) = grams

- Appearance of dose-related findings
  - ➡ However, findings were either not statistically significant or deemed not biological significant due to the magnitude of the effect

Main Study: Fetal Findings

- External:
  - Single or sporadic incidences/findings
- Visceral:
  - Single or sporadic incidences/findings
- Head:
  - Single or sporadic incidences/findings
- Skeletal:
  - Exposure-related increase in the percent of fetuses with lumbar rudimentary ribs
    - Common variation observed in this strain of rat which is reported to be reversible and of limited toxicological relevance

Main Study Summary

- TCPP was well tolerated and there were no maternal treatment-related effects on mortality or body weights during gestation
  - Clinical observations were of low incidence and limited the 650 mg/kg group
- Dose-related increase in maternal liver weights
  - At 650 mg/kg, absolute and relative liver weights were increased ~ 26%
- No treatment-related effects on uterine or litter parameters, including implantations, litter size, live fetuses per litter or fetal weight
- Fetal examination findings were:
  - Singular or sporadic incidences
  - Variations of limited toxicological relevance (e.g., lumbar rudimentary ribs)

Conclusion

Under the conditions of this prenatal study:

- ***No evidence*** of developmental toxicity of TCPP in Hsd:Sprague Dawley SD rats administered 162.5, 325, or 650 mg/kg in the absence of overt maternal toxicity

Questions?