Karlsruhe Institute of Technology

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Tricresyl phosphate and organophosphate-induced delayed neuropathy

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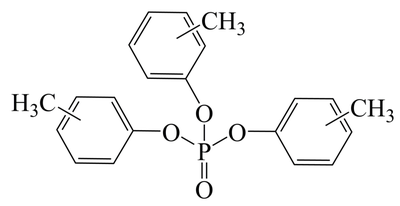
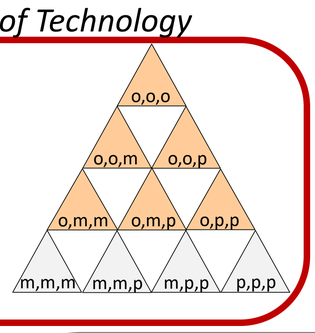
o-isomers:
no intended application but impurity in commercial tricresyl phosphate mixtures





m- and p-isomers:
>98% in commercial mixtures, used in jet engine oil

o-isomers

Human poisoning (examples):

1930s (USA): after consumption of `Jamaika Ginger Extract´ 20,000-50,000 cases

1959 (Morocco): 10,000 cases after using cooking oil contaminated with jet engine oil

Abb. 1

Affected people suffer from paralysis of the distal extremities in particular legs and feet. The symptoms correspond to the nerve disease **OPIDN** (see next box).

Identified cause: **contamination with o-isomers**

⇨ Reduction of o-isomers content in commercial tricresyl phosphate mixtures to <2% *(Duarte et al. 2017)*

m- and p-isomers

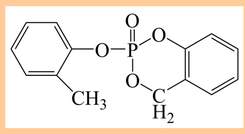
- **No neurotoxic potential** in chickens, cats, rodents
- Not irritating, no genotoxic / carcinogenic potency
- **Rats and Mice** (oral, 2 years, *NTP 1994*):
  rats **ovaries** hyperplasia interstitial cells
  adrenals higher grade of cytoplasmic vacuolation
  mice **liver** ceroid pigmentation, foci, changed fat cells
  NOAEL: **7 mg/kg bw/day**

⇨ **MAK value 5 mg/m³ (I) for m- and p-isomers**

Pregnancy Risk Group C

OPIDN („organophosphate-induced delayed neuropathy“):
Muscle weakness resulting in paralysis of the distal extremities accompanied with degeneration of the peripheral nerves (spinal and sciatic nerves).

Main **metabolite** of o-isomers: o-cresyl-saligenin phosphate (CBDP):



- more toxic than the parent compound
- strong inhibitor of esterases, in particular the neuropathy target esterase

Neuropathy target esterase (NTE) (*Glynn et al. 2013)*:

- involved in phosphatidylcholine homeostasis of the membrane and secretory mechanism of the nerve cell
- active site serin is inhibited by phosphorylation
- activity inhibition of 50-70% is necessary for neurotoxic symptoms

Mutation in the **human NTE-gene** results in progressive weakness of the distal extremities *(Rainier et al. 2011)*.

Cholinesterases are not involved in OPIDN caused by o-tricresyl phosphate.

Chickens and **cats** are much more susceptible to OPIDN and NTE effects and more similar to humans than rodents.

Animal data tri-o-isomer

Cats (dermal, 90 days, *Abou-Donia et al. 1986*):
Legs weakness, ataxia
NOAEL: 0.5 mg/kg bw/day
LOAEL: 1 mg/kg bw/day

Chickens (♀ gavage, 90 days, *Prentice & Majeed 1983*):
CNS and PNS degeneration, ataxia
NOAEL: 1.25 mg/kg bw/day
LOAEL: 2.5 mg/kg bw/day

Corresponding concentration in the air at the workplace:
Cat NOAEL 0.5 mg/kg bw → 2.5 mg/m³
Chicken NOAEL 1.25 mg/kg bw → 3.0 mg/m³
→ **calculated limit value** 0.2 mg tri-o-isomer/m³ ≙ **0.01 ml/m³**

Animal data mono-, di- and tri-o-isomers

Chickens (oral, mixture in jet engine oil, 90 days, *Freudenthal et al. 1993*):
NOAEL: -
LOAEL: 0.24 mg o-isomers (in jet engine oil)/kg bw/day

Chickens (oral, single dose, *Henschler 1958*):

isomer	LOAEL (mg/kg bw)	NOAEL (mg/kg bw)
ooo	480	30
oop, oom	120	30
omp, omm	30	-

MAK value o-isomers

- Calculated limit value for tri-o-isomer is 0.01 ml/m³
- **Higher toxicity** of **mono-** and **di-o-isomers** compared to tri-o-isomer: ratio **10** (mono) : **5** (di) : **1** (tri)
- Tricresyl phosphate solutions contain an **unknown amount of mono- or di-o-isomers**

⇨ **MAK value 0.001 ml/m³ for tricresyl phosphate o-isomers,** to consider higher toxicity of mono- and di-isomers
Carcinogen Category 3 B (DNA adducts), Pregnancy Risk Group D (no data)

Tri-o-cresyl phosphate exposure in cabin air is nowadays below the limits for analytical detection (LOD 0,5 ng/m³, *de Boer et al. 2015*).

References: Abou-Donia MB, Trofatter LP, Graham DG, Lapadula DM (1986) Electromyographic, neuropathologic and functional correlates in the cat as the result of tri-o-cresyl phosphate delayed neurotoxicity. Toxicol Appl Pharmacol 83: 126–141; de Boer J, Antelo A, van den Veen I, Brandsma S, Lammertse N (2015) Tricresylphosphate and the aerotoxic syndrome of flight crew members - current gaps in knowledge. Chemosphere 119: 558–561; Freudenthal RI, Rausch L, Gerhart JM, Barth ML, Mackerer CR, Bisinger EC (1993) Subchronic neurotoxicity of oil formulations containing either tricresyl phosphate or tri-orthocresyl phosphate. J Am Coll Toxicol 12: 409–416; Glynn P (2013) Neuronal phospholipid deacylation is essential for axonal and synaptic integrity. Biochim Biophys Acta 1831: 633–641; Henschler (1958) Die Trikresylphosphatvergiftung. Klin. Wochenschr 36: 663-674; NTP (1994) https//ntp.niehs.nih.gov/ntp/htdocs7lt.rpts/tr433; Prentice DE, Majeed SK (1983) A subchronic study (90 day) using multiple dose levels of tri-orthocresyl phosphate (TOCP): some neuropathological observations in the domestic hen. NeuroToxicol 4: 277–282; Rainier S, Albers JW, Dyk PJ, Eldevik OP, Wilcock S, Richardson RJ, Fink JK (2011) Motor neuron disease due to neuropathy target esterase gene mutation: clinical features of the index families. Muscle Nerve 43: 19–25; Roberts NL, Fairley C, Philipps C (1983) Screening, acute delayed and subchronic neurotoxicity studies in the hen: measurements and evaluation of clinical signs following administration of TOCP. NeuroToxicology 4: 263–270; Winder C, Balouet JC (2002) The toxicity of commercial jet oils. Environ Res 89: 146–164
Abb.1: https://mindhacks.com/2011/06/30/the-ginger-jake-poisonings/

Further information: www.dfg.de/en/mak

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