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ENVIRONMENTAL AFFAIRS
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Document Control Office
Office of Pesticides and Toxic Substances
U.S. Environmental Protection Agency
401 M. Street, S.W.
Washington, DC 20460

TSCA Section 8(e) Notification
Tricresyl Phosphate (TCP)
CAS Registry Number 1330-78-5

Dear Sir:

As part of its ongoing program of evaluating petroleum products, streams and components, the Mobil Environmental and Health Science Laboratory (MEHSL) has investigated the toxicity of a generic jet engine oil and one of its components, tricresyl phosphate (TCP). The oil contained certain additive components at concentrations representative of a cross section of those in commercial production.

Our research showed that repeated applications of the generic jet engine oil containing 3% TCP (one dermal application/day, 5 days/week, for 90 days) to male and female Sprague-Dawley rats decreased the activities of both serum and erythrocyte cholinesterase (Table 1). A follow-up study, designed to identify the component causing cholinesterase inhibition, showed that the TCP additive was entirely responsible (Table 2). An additional acute study, performed in male Long-Evans rats, showed that single doses of TCP or TOCP, administered either orally or dermally, inhibited both serum cholinesterase and brain neuropathy target esterase (neurotoxic esterase; NTE) (Table 3). Inhibition of NTE is highly correlated with induction of organophosphorus induced delayed neurotoxicity (OPIDN). Surprisingly, there was very little difference between the activities of TCP and TOCP; the TCP manufacturer's product safety information sheet indicated that TOCP content is less than 0.1%.

We are under the impression that a commonly held opinion is that TCP with TOCP levels below 1.0% is not neurotoxic. Our results indicate that the TOCP level in TCP is not a reliable predictor of potential neurotoxicity.

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Four batches of the TCP additive used in the tests described in Tables 1-3 and three other TCP samples also were evaluated for acute cholinesterase and NTE inhibition (Table 4). All showed significant inhibitory effects that, on repeated administration, would be expected to result in neurotoxicity. All materials were derived from cresylic acids produced as a byproduct of petroleum refining. Other commercially available TCPs are prepared from synthetically derived materials, which can provide better control of the content of potentially neurotoxic components.

A thorough literature review (see Attachment I) revealed that the neurotoxic properties of commercial TCP are known, but that there is confusion over the appropriateness of using the TOCP level as an indicator of neurotoxic potential. After considering the weight of all available evidence, both published and our new data, we concluded that EPA and other users of TCP as a lubricant additive should be informed of our results.

DESCRIPTION AND USES OF TCP

TCP is used as an anti-wear agent in jet engine oils, and is required to meet both military and commercial jet engine builder's specifications. It is used as a minor component (< or ≈ 2%) in certain mineral oil based lubricants. Certain fire resistant hydraulic fluids are based on 100% TCP, some of which are synthetically derived.

HAZARD COMMUNICATION

Mobil is unaware of any neurotoxic effects on humans having been caused by exposure to jet engine oils in their intended application. However, we are revising our Material Safety Data Bulletins and product labels to inform employees and customers of the information reported herein. We also are sending copies of this letter to OSHA, to other users and suppliers of TCP and to appropriate trade associations (API, CONCAWE, IFIECA, CMA and SOCMA).

Sincerely,

J.P. McCullough

CRM/dg
Attachments

This report is being made in compliance with Section 8(e) of the Toxic Substances Control Act (15 U.S.C. 2607), pursuant to our understanding of the statement of Interpretation and Enforcement Policy (43 Fed. Ref. 11110 et. seq.). It has been compiled based on information available within the time period given. While we believe the tests reported were properly performed, no representation can be made as to their accuracy of content. The corporation and individual signator also reserve the right to supplement any or all of the data contained herein and to revise or amend any conclusion drawn therefrom.

Table 1

Effects of Subchronic Administration of Generic Jet Engine Oil Containing 3.0% Tricresyl Phosphate[1] (SAMPLE A) on Mean Serum and Erythrocyte Cholinesterase Activities[2]

Study No.: 60431

Mean Cholinesterase Activity

Parameter (Units)	Group No.: Dose (mg/kg/day):	1 Control	2 600	3 2000
A Males				
Week 5 Serum (IU/l)		499	381[3]	304[3]
(% Inhibition)		0	24	39
Week 13 Serum (IU/l)		479	246[3]	174[3]
(% Inhibition)		0	49	64
Week 13 Erythrocyte (IU/l)		1050	938[4]	840[3]
(% Inhibition)		0	11	20
B Females				
Week 5 Serum (IU/l)		2833	1902[3]	1272[3]
(% Inhibition)		0	33	55
Week 13 Serum (IU/l)		4613	2352[3]	1063[3]
(% Inhibition)		0	49	77
Week 13 Erythrocyte (IU/l)		1054	890	812[3]
(% Inhibition)		0	11	23

[1] See Table 4
[2] Ten male and ten female Sprague-Dawley rats received dermal applications of the experimental oil 5 days/wk for 90 days.
[3] Statistically different from control ($P<.05$).
[4] Mean value for nine rats.

Table 2

Effects on Serum Cholinesterase (ChE) Activities in Female Sprague-Dawley Rats at 24 Hours After A Single Oral Administration of Generic Jet Engine Oil (With and Without Tricresyl Phosphate (TCP)[1]) Triorthocresyl Phosphate (TOCP) and TCP

Study No.: 61924

Test Materials	Number of Rats	Dose (mg/kg)	Serum ChE Activity (% inhibition)
Jet Oil without TCP	5	2000	8
Jet Oil with 3% TCP	5	2000	25[2]
TCP	5	60	45[2]
Triorthocresyl Phosphate (positive control)	5	60	54[2]

[1] Sample A – See Table 4
[2] Statistically significant inhibition ($p<.05$).

Table 3

Effects on Brain Neuropathy Target Esterase (NTE) and Serum Cholinesterase (ChE) in Male Long-Evans Rats Following A Single Oral or Dermal Exposure to TCP (Sample A)[1] or Triorthocresyl Phosphate (TOCP)

Study No.: 00116-2

Test Materials	N	Route	Dose[2] (mg/kg)	NTE[3] (% inhibition)	Serum ChE[3] (% inhibition)
TCP	5	Oral	2320	83 (44 hr)	82 (24 hr)
TOCP	5	Oral	2320	97 (44 hr)	96 (24 hr)
TCP	3	Dermal[4]	2320		44 (24 hr) 65 (48 hr) 66 (96 hr)
				55 (day 6)	65 (day 6)
TOCP	4	Dermal[4]	2320		36 (24 hr) 58 (48 hr) 75 (96 hr)
				72 (day 6)	78 (day 6)

[1] See Table 4.
[2] The dose level was identical to that used by Padilla and Veronesi (1985) for male Long-Evans rats.
[3] All inhibitons are statistically significant ($p<.05$).
[4] The experiments were performed using nonocclusive (perforated) glass cells covering the entire dosed area.

Table 4

Serum Cholinesterase (ChE) and Brain
Neuropathy Target Esterase (NTE) Inhibition Following
A Single Oral Dose of 2.0 g/kg Tricresyl
Phosphate to Long-Evans Rats

Study No.: 62668

TCP Samples Tested	ChE Inhibition (%)[1]	NTE Inhibition (%)[1]
Sample A		
Batch 1	62	52
Batch 2	69	55
Batch 3	73	56
Batch 4[2]	75	76
Sample B[3]	83	43
Sample C	63	74
Sample D	78	77
Triorthocresyl Phosphate[4]	94	93

[1]Values presented are means for at least five rats.
[2]Batch 4 is the material used for the experiments reported in Tables 1 - 3.
[3]A high purity tricresyl phosphate which we believe to be manufactured from naturally sourced cresylics but containing 98.0% meta/para isomers.
[4]Positive control; 97% pure.

Historical:

TCP became of interest toxicologically in 1930 when partial paralysis in approximately 50,000 Americans occurred from its presence as an adulterant in extracts of Jamaica ginger [1,2]. Smith et al. [1] studied the technical grade of TCP used in the ginger extract in animals and produced the same type of neurological symptoms observed in humans. During the 1930s, TCP was considered to be composed of only three main phosphoric acid esters (viz., tri-ortho-cresyl phosphate [TOCP], tri-meta-cresyl phosphate [TMCP], and tri-para-cresyl phosphate [TPCP]). Subsequent work by Smith et al. [3] demonstrated that TOCP was neurotoxic in animals and could account for the partial paralysis observed in humans from the ingestion of the ginger extract [Smith estimated the TOCP content of the adulterated ginger to be approximately 2.0%]. TMCP and TPCP were found not to be neurotoxic. On the basis of these findings, TOCP was considered to be the only neurotoxic component of TCP.

Over the years, widespread epidemics following the ingestion of TCP and/or TOCP and closely-related phosphate esters in adulterated foods and cooking oils have been reported [2]. In a few instances, neurotoxicity has occurred as a result of industrial exposure via inhalation and absorption through the skin [4,5]. In the majority of these poisonings, not only are the isomers of TCP usually present but also several related compounds, such as xylenyl phosphates, and ethylphenyl phosphates, which are also toxic and share responsibility for the neurotoxicity [5]. For this reason the term "tri-aryl phosphate poisoning" was introduced.

Many reviews on the etiology and postulated mechanisms of organophosphorus-induced delayed neurotoxicity (OPIDN) in both humans and animals have been published [6-7].

Dermal Absorption:

In 1943, Hodge and Sterner [8] studied the skin absorption of TOCP containing radioactive phosphorus in humans and dogs. The human subjects applied TOCP to the palms of both hands for a 3.5 hrs exposure, prior to its removal with an appropriate solvent. TOCP was also painted on the abdominal surface of lightly anesthetized female dogs for a continuous exposure of 25.25 hours. TOCP was observed to be readily absorbed through the palmar skin of human hands and through the abdominal skin of dogs. These data indicate that the magnitude of absorption of TOCP through skin is such that a real hazard exists in industrial operations permitting a considerable or repeated exposure to this substance.

Carpenter and others [9], studied the effects of triaryl phosphate (TAP; ortho-cresol content of cresylic acid mixture prior to esterification was kept below 1.5% of the total; the term TCP has also been used to describe this preparation) after dermal administration in rabbits. TCP was observed to cause cholinesterase (ChE) inhibition and a questionable delayed hind limb weakness in some rabbits.

Litau [10] studied the skin resorption of 4.0% technical TCP in male mice after 4 hrs of contact and in guinea pigs after 30-days of contact. Treated miced (4 hrs of contact) exhibited neurotoxic effects (i.e., motor depression and dull reflexes to pain), but no visible skin alterations. Serum ChE activity was reduced in animals treated with TCP. Thirty (30) days of exposure to TCP in Guinea pigs also caused neurotoxic and other affects (i.e., disturbances in motor coordination, reduced ChE activity, and reduced weight gain). Skin effects (i.e., desquamation, thickening of skin and basal and keratic layers, enlargement of hair bulbs, cell infiltration, and edema) were also seen at the application site.

Delayed paralysis and spinal cord degeneration were reported after a single topical application of TCP on the combs of hens [11]. Ahmed and Glees [12] also demonstrated delayed paralysis and spinal cord, axonal, and peripheral nerve degeneration after dermal application of TCP (TOCP content not given) for ten days in primates (slow loris). Attempts to induce paralysis in other primates (monkeys and baboons) have been unsuccessful.

In 1957, Tabershaw and Klainfeld [13] performed a clinical study of workers exposed via skin or atmospheric contamination to TCP (containing up to 20.0% TOCP, in concentrations from 0.27 to over 1 mg/m^3) during its manufacture over an average duration of nine years. The workers exhibited no chronic adverse effects on health. However, there was some evidence of absorption and some aggravation of gastrointestinal and neuromuscular symptoms which were functional and mild. Plasma ChE levels were also found to be significantly below normal levels. Similar ChE findings were reported aboard a Naval ship (USS Shangri La) [14]. In another study aboard the USS Leyte, Baldridge et al. [14] observed no toxic effects (including no adverse effects on plasma or red cell ChE levels) from skin or atmospheric exposure to TCP in a hydraulic fluid. This study was conducted under conditions which were intended to minimize the potential exposure hazard (i.e., full ventilation, enforced personal hygiene, etc.).

These scientific publications indicate that TCP can penetrate the skin and cause neurotoxic effects (viz., ChE inhibition and OPIDN).

Neurotoxicity:

As previously mentioned, TOCP is one of the esters present in commercial TCP and the toxicity of TCP has often been considered to be solely determined by the amount of o-cresol present in the raw material from which the esters are made. In 1958, Henschler [15] discussed the toxicity of the "older" technical preparations of TCP (believed to contain 30% o-cresyl) and pointed out that, the toxicity of these preparations was assumed to be due to the tri-ortho-cresyl constituent, however, his new data indicates that pure tri-ortho-cresyl ester was the least toxic of all the orthocresyl esters. He concluded that "Modern" TCP preparations containing only 3.3% of o-cresyl were found to be only slightly toxic. Based on this data, limitation of the ortho-cresol content of the crude cresylic acid used in the manufacture of TCP has been followed by a notable absence of clinically discernible toxic effects. This has led some countries to demand that the cresol fraction used in the preparation of TCP should contain not more than 3.0% ortho-cresol. However, this provision has not abolished the toxicity associated with commerical TCP [2].

In 1956, Hines et al. [16] demonstrated that triaryl phosphate containing only one or two ortho-cresol moieties possess toxicity of the same order and the discrepancy between the experimental toxicity of a TCP preparation and its ortho-cresol content, suggests that there are other components of equal or greater activity. This observation was supported by Carpenter et al. [9] with a sample of TCP containing < 1.5% TOCP. They concluded that there were other substances present in TCP which have similar paralytic activity or which markedly potentiate the activity of TOCP. Friess et al. [17] also concluded that TCP (containing trace amounts of TOCP) had paralytic activity and that the chemical control of the concentration of TOCP in TCP does not suffice to stabilize the toxicity.

As a result of the inherent toxicity of TCP, Bondy et al. [18] attempted to prepare a non-neurotoxic phosphate plasticizer from either TCP or tri-xylenyl phosphate (TXP). They demonstrated that the removal of the neurotoxic o-cresyl esters failed to render the product non-neurotoxic (paralytic activity in chickens). This was particularly surprising because the sample was believed to be

composed of only dimethylphenol derivatives and the non-neurotoxic phosphates of the meta- and para-cresols. The dimethylphenol derivatives were tested and found to be non-neurotoxic except in massive doses. Further studies demonstrated that tri-ortho-ethylphenyl ester was non-neurotoxic, but the mono- and di-ortho-ethylphenyl phosphates were highly neurotoxic. In a similar fashion, tri-ortho-n-propylphenyl phosphate was shown to be non-neurotoxic, the esters containing one or two ortho-propylphenyl groups were neurotoxic. Additional, experiments also showed that tri-meta-ethylphenyl phosphate was non-neurotoxic, while the tri-para-ethylphenyl phosphate was found to be neurotoxic. These authors concluded that the neurotoxicity of TCP is due not only to the presence of phosphate esters containing one, two or three ortho-cresyl groups, one or two ortho-propylphenyl groups, and one or two ortho-ethylphenyl groups, but also tri-para-ethylphenyl phosphates. The tri-xylenyl phosphate has also been judged to have some neurotoxic effects.

TCP in edible oils, whether or not it contains TOCP, has also been shown to be injurious to health in humans [19]. Recently, a case of severe acute intoxication in a 4.5 year-old child following ingestion of a lubricant containing TCP has been reported [20]. Clinical findings in this child were acute gastrointestinal symptoms, delayed cholinergic crisis and neurological toxicity. Blood samples revealed no evidence of TOCP. Gas chromatography-mass spectroscopy analysis of the lubricant indicated the presence of multiple tri-amyl-phosphates, including triphenyl and tricresyl phosphates. TOCP was not identified. Other phosphate esters were present but could not be identified.

Many organophosphorus esters are inhibitors of ChE activity in humans and experimental animals. The effects of commercial TCP on ChE activity have been reported [6, 7, 21]; in most cases, serum ChE levels were found to be significantly below normal/control ChE values. Oishi et al. [22], observed no inhibition of ChE activity in Wistar rats fed a diet containing 0.0 or 0.5% TCP for 9 weeks.

Although numerous investigators use the reduction of ChE activity, following the administration of triarylphosphates, as an indicator of neurotoxicity, there is no consistent correlation between anti-ChE activity and neuroparalytic activity [9,6,7,16,21]. Not all ChE inhibitors cause OPIDN but all agents which produce OPIDN do inhibit ChE.

The MSDS issued for TCP SYN-O-AD® indicates that the product shows NTE inhibition after large single oral doses in hens. We are not aware of any published reports that rat brain NTE is inhibited by commercial TCP by any route of administration. Padilla and Veronesi [24], however, have demonstrated NTE inhibition in rats exposed to a single oral dose of TOCP.

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Table 2. Subset of Chemicals That Could Be Present In The Aircraft Cabin Environment and Measurement Methods.

	USEPA 1999a:	TO-10	TO-11	TO-13	TO-14	TO-15	TO-17
	ASTM 1999:	D 4861	D 5197	D 4861	D 5466	D 5466	D6196
	Collection:	PUF Tube	DNPH	PUF Tube	Canister	Canister	Sorbent Tube
	Analysis:	GC/MS	HPLC	GC/MS	GC/MS	GC/MS	GC/MS, FID...
CASRN	CHEMICAL	SVOCs	Aldehydes	SVOCs	VOCs	VOCs	VOCs
75-07-0	Acetaldehyde (Ethanal)		✔			✔	✔
67-64-1	Acetone		✔				
107-02-8	Acrolein					✔	✔
71-43-2	Benzene					✔	✔
64-17-5	Ethyl Alcohol (Ethanol, Ethanole)					✔	✔
50-00-0	Formaldehyde	✔					
110-54-3	N-Hexane					✔	✔
75-09-2	Methylene Chloride						
123-38-6	Propanaldehyde						
127-18-4	Tetrachloroethene				✔	✔	✔
3163-58-2	TOCP (Triorthocresylphosphate)						
108-88-3	Toluene						
1330-20-7	Xylenes					✔	✔