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Tricresyl Phosphate Neurotoxicity Potential

George William Sherk

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I can't eat, I can't talk
Been drinking mean Jake,
Lord now I can't walk.
Ain't got nothing, 'count to lose
'Cause I'm a Jake walking papa
with the Jake Walk Blues.

Introduction

The Allen Brothers recorded "Jake Walk Blues" in May, 1930. "Jamaican Ginger" (or "Ginger Jake" or simply "Jake") was an over-the-counter remedy whose success in treating a variety of ailments may have resulted from its 70-80% alcohol content.[1] Such "medicinals" were popular during Prohibition, especially among the poor of the rural South and Midwest.[2]

Hub Products Corporation produced one particular batch of "Jake" (enough for 640,000 two-ounce bottles) using Lindol instead of castor oil as a solvent. The Lindol contained tri-*ortho*-cresyl phosphate (TOCP), a neurotoxicant. As a result, between 1930 and 1931, an estimated 40,000 to 50,000 people ingested "Jake" contaminated with TOCP, the consequences of which, "a severe central peripheral distal axonopathy," are reflected in the Allen Brothers' song.[3]

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1 *See* Alan D. Woolf, *Ginger Jake and the Blues: A Tragic Song of Poisoning*, 37 Vet. & Hum. Tox. 252 (1995).

2 *Id*; *see also* Douglas C. Anthony, Thomas J. Montine & Doyle G. Graham, *Toxic Responses of the Nervous System*, in Casarett & Doul's Toxicology: The Basic Science of Poisons (6th ed., 1996).

3 *Supra* note 1.

These consequences resulted from the process by which "Jake" was produced. While "Jake" has long since departed the marketplace, there are other products that expose individuals to TOCP. Once again, TOCP exposure may result from the process by which specific products are manufactured.

One of these products is tricresyl phosphate (TCP), a nonflammable, nonexplosive, colorless, viscous fluid.[4] It is utilized as a vinyl plasticizer, a fire retardant, a high performance lubricant and as an anti-wear additive.[5] Mostly, TCP was developed to meet aviation safety and performance requirements. Consequently, it is a common component of a variety of aircraft lubricating and hydraulic fluids.[6]

In addition, TCP is used in cutting oils, machine oils, extreme high pressure fluids, automobile transmission fluids and certain cooling lubricants.[7] It is also used in the making of synthetic leather and polyvinyl acetate products as well as in the manufacture of the interior components of automobiles. In fact, "TCP can evaporate from automobile upholstery fabrics and condense on the interior surface of a relatively cool window."[8]

The production process for commercial grade TCP utilizes technical grade cresols (methyl phenols) produced through the distillation of hydrocarbons. Because commercial grade TCP utilizes natural sources of cresols, a number of unwanted components may be contained in the final product. These unwanted components may include up to ten TCP isomers, one of which is TOCP.

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4 *See* World Health Organization (WHO) Working Group, *Tricresyl Phosphate*, Env. Health Criteria at 110 (1990).

5 *Id.; see also* J.R. Latendresse, C.L. Brooks & C.C. Capen, *Toxic Effects of Butylated Triphenyl Phosphate-Based Hydraulic Fluid and Tricresyl Phosphate in Female F344 Rats*, 32 Vet. Path. 394 (1995); *see also* Michael P. Marino, *Phosphate Esters*, in Synthetic Lubricants and High-Performance Functional Fluids (1992); *see also* Hideo Kurebayashi, Akira Tanaka & Tsutomu Yamaha, *Metabolism and Disposition of the Flame Retardant Plasticizer, Tri-p-cresyl Phosphate, in the Rat*, 77 Tox. & App. Pharm. 395 (1985).

6 *See supra,* Marino.

7 *See* WHO, *supra* note 4; *see also* National Toxicology Program (NTP) Working Group, *Toxicology and Carcinogenesis Studies of Tricresyl Phosphate in F344/N Rats and B6C3F1 Mice (Gavage and Feed Studies)*, 433 Nat'l Tox. Prog. Tech. Rep. (1994).

8 WHO, *supra* note 4.

This report addresses the potential neurotoxicity of the ten isomers that may be contained in commercial grade TCP. The process by which the isomers are created is described in the following section. Section III reviews the absorption, distribution, metabolism and excretion of the isomers. The potential neurotoxicity of isomers containing an *ortho*-methyl group is reviewed in Section IV and discussed in Section V. Conclusions are presented in Section VI.

The Production Process

The production process begins with the distillation of hydrocarbons, usually coal tar or the residue from coke ovens and petroleum refining.[9] Primary distillation of these hydrocarbons produces crude cresylic acids (or "tar acids"). Fractionation of these acids then yields crude phenol (including fluids high in *ortho* cresol content), a mixture of isomeric cresols and a crude *meta/para* cresol fraction.[10]

Redistillation of the *meta/para* cresol fraction yields two cresol isomers, either a product containing at least 50% *meta* cresol or a product containing 58%-60% *meta* cresol and 40%-42% *para* cresol. Both of these products may contain small amounts (<1%) of *ortho* cresol. A number of other substances may be present, depending on the temperature of distillation (different substances having different boiling points), the specific distillation process utilized and the content of the hydrocarbon feedstock.[11] The substances likely to be present in the two cresol isomers include *ortho* cresol (2-methyl phenol), *meta* cresol (3-methyl phenol), *para* cresol (4-methyl phenol), 2, 3-xylenol (2, 3-dimethyl phenol), 2, 4-xylenol (2, 4-dimethyl phenol), 2, 5-xylenol (2, 5-dimethyl phenol), 2, 6-xylenol (2, 6-dimethyl phenol), 3, 4-xylenol (3, 4-dimethyl phenol), 3, 5-xylenol (3, 5-dimethyl phenol), *ortho* ethyl phenol (2-ethyl phenol), *meta* ethyl phenol (3-ethyl phenol), *para* ethyl phenol (4-ethyl phenol) and 2, 4, 6-trimethyl phenol.[12]

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9 *See id.*

10 Proprietary source.

11 Marino, *supra* note 5.

12 Proprietary source.

After the redistillation process is complete, either of the two cresol isomers is combined with phosphorus oxychloride ($POCl_3$) to produce commercial grade TCP.[13] As noted above, because the two cresol isomers are derived from various natural sources, a number of unwanted components may be contained in the isomers. In essence, "the composition of the final product depends on the isomeric composition of the cresol preparation[.]"[14]

These unwanted components may include as many as ten "structurally distinguishable triesters of cresol and phosphoric acid."[15] The isomers are distinguished by the location of the methyl group on the phenyl ring in any of the *ortho*, *meta* or *para* positions.[16] Figures 1 through 3 represent pure tri-isomer triesters:

Figure 1: Tri-*ortho*-cresyl phosphate (TOCP)

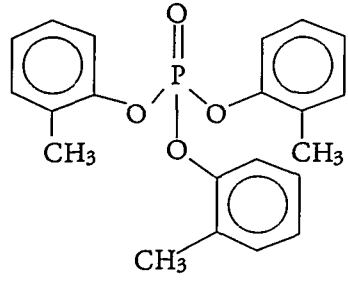
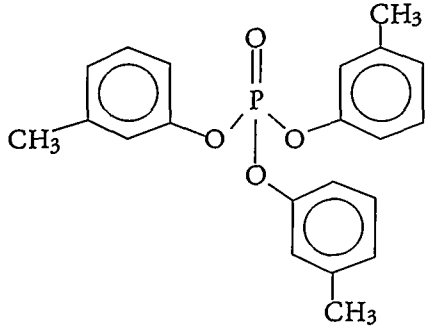
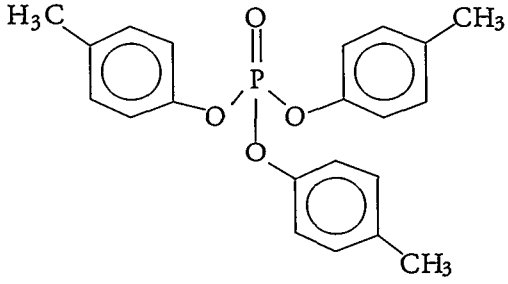


Figure 2: Tri-*meta*-cresyl phosphate (TMCP)



13 WHO, *supra* note 4; *see also* NTP, *supra* note 7.
14 NTP, *supra* note 7.
15 *Id.*
16 Marino, *supra* note 5.

Figure 3: Tri-*para*-cresyl phosphate (TPCP)



Figures 4 through 9 are mixed di- and mono-isomers:

Figure 4: Di-*ortho*-cresyl-*meta*-cresyl phosphate

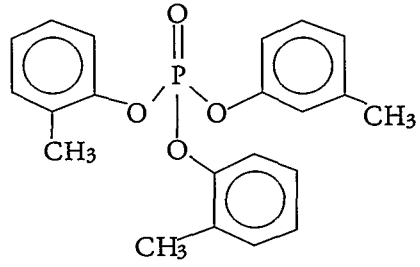


Figure 5: Di-*ortho*-cresyl-*para*-cresyl phosphate

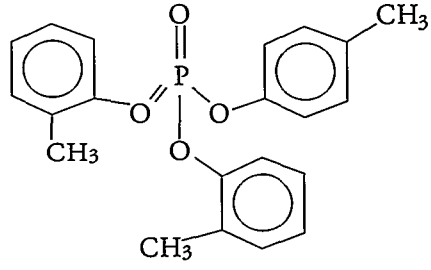


Figure 6: Di-*meta*-cresyl-*ortho*-cresyl phosphate

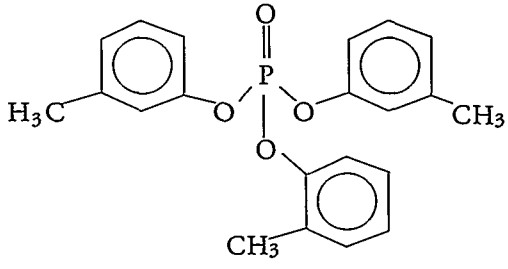


Figure 7: Di-*meta*-cresyl-*para*-cresyl phosphate

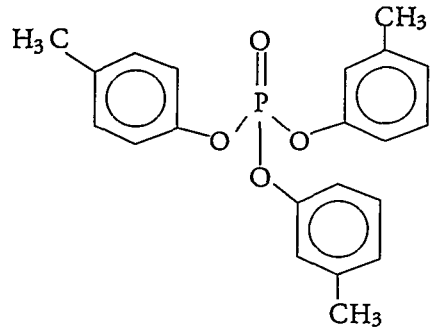


Figure 8: Di-*para*-cresyl-*ortho*-cresyl phosphate

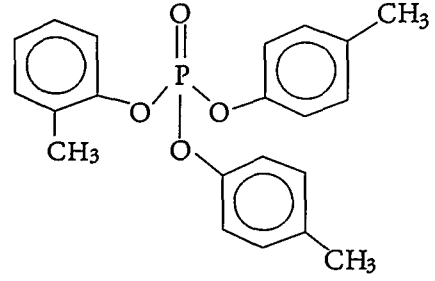
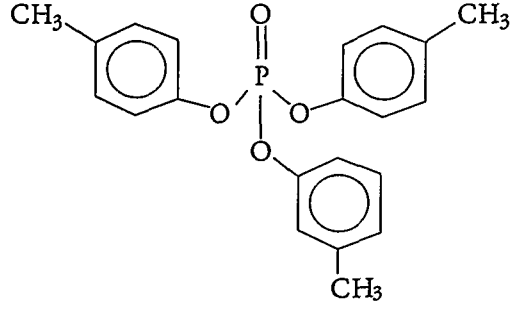
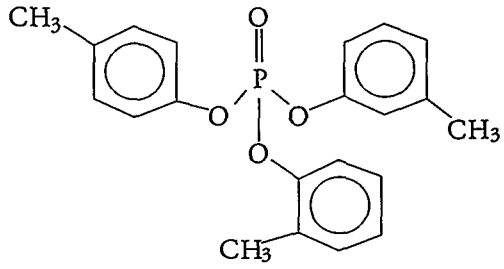


Figure 9: Di-*para*-cresyl-*meta*-cresyl phosphate



Last is a mixed tri-isomer:

Figure 10: *Ortho*-cresyl-*meta*-cresyl-*para*-cresyl phosphate



Absorption, Distribution, Metabolism and Excretion

Understanding the absorption, distribution, metabolism and excretion of organophosphates such as TCP is critical to understanding the delayed neuropathic effects that may result from exposure to these compounds.[17] Unfortunately, of the ten TCP isomers, virtually all studies conducted to date have focused on the pure tri-isomers, with TOCP (Figure 1) receiving significantly greater attention than either TMCP (Figure 2) or TPCP (Figure 3). There are very few studies that "attempt[] to characterize the metabolism of tricresyl phosphate prepared from mixed isomers."[18]

Absorption

TOCP, TMCP or TPCP may enter the body by a number of pathways. A primary means is absorption through the skin.[19] Animal studies have shown that TOCP is readily absorbed following dermal application.[20] With regard to TMCP and TPCP, "the similarity of structure and physical properties (solubility, etc.) make it likely that these compounds are also absorbed through the skin."[21]

All three isomers may be absorbed through both the lungs and the gastrointestinal tract.[22] There have been multiple cases of accidental

17 WHO, *supra* note 4.

18 NTP, *supra* note 7.

19 *See* Latendresse, *supra* note 5; *see also* WHO, *supra* note 4; *see also* NTP, *supra* note 7; *see also* Mohamed B. Abou-Donia & Daniel M. Lapadula, *Mechanisms of Organophosphorus Ester-induced Delayed Neurotoxicity: Type I and Type II*, 30 Ann. Rev. Pharm. & Tox. 405 (1990).

20 *See* WHO, *supra* note 4; *see also* NTP, *supra* note 7.

21 *See* NTP, *supra* note 7.

ingestion of hydraulic fluid, lubricating oil or mineral oil containing TCP. Several incidents have also been reported where cooking oil or flour contaminated with hydraulic fluid or lubricating oil led to the ingestion of TCP.[23]

Distribution

The NTP Working Group noted that TOCP, TMCP and TPCP are distributed rapidly to the liver and muscle. Thereafter, all three isomers are redistributed to adipose tissue and to skin.[24]

Citing an earlier study, the WHO Working Group noted distribution of TOCP in the following descending order: Liver > blood > kidney > lung > muscle or spinal cord > brain or sciatic nerve. Ten days post-exposure, the highest levels of TOCP were found in the bile, gall bladder, urinary bladder, kidney and liver with only small amounts being detected in the spinal cord or brain.[25]

Metabolism

The initial step in the metabolism of TOCP appears to be the oxidation of one or more of the *ortho*-cresyl groups to produce *ortho*-hydroxy benzyl alcohol (saligenin) residue. This reaction, which occurs in the liver, appears to be catalyzed by the microsomal mixed-function oxidase system. Once this reaction has occurred, the *ortho*-hydroxy benzyl alcohol (saligenin) residue cyclizes via an internal group displacement reaction and displaces the remaining *ortho*-cresyl groups.[26] This process leads to the formation of saligenin cyclic *ortho*-totyl phosphate (cyclic phosphate), a relatively unstable neurotoxic metabolite that is hydrolyzed rapidly to inactive metabolic products and does not bioaccumulate in the body.[27] It is interesting to note that animal studies (utilizing chickens) show the metabolite (saligenin cyclic *ortho*-totyl phosphate) is at least five times more toxic than the parent compound (TOCP).[28]

22 *See* Latendresse, *supra* note 5.
23 *See* WHO, *supra* note 4; *see also* NTP, *supra* note 7.
24 *See* NTP, *supra* note 7.
25 *See* WHO, *supra* note 4.
26 *See* NTP, *supra* note 7.
27 *See* WHO, *supra* note 4.
28 *Id.*

The process by which saligenin cyclic *ortho*-totyl phosphate (cyclic phosphate) is formed does not occur when TPCP is metabolized. This result is because the cyclization process described above does not occur, apparently because the methyl group is positioned so that the resulting *para*-hydroxy benzyl alcohol residue cannot participate in the cyclization process (see Figure 3).[29]

Though the metabolism of TMCP has not been studied extensively, the position of the methyl group in TMCP is similar to the position of the methyl group in TPCP (see Figure 2). Consequently, it may be presumed that the metabolic processes are also similar.[30]

Excretion

Animal studies indicate that TOCP is excreted primarily in the urine (70%) within 24 hours of dosage. With regard to TPCP, the final product of the metabolic process is *para*-hydroxy benzoic acid, excreted primarily in the urine. Animal studies, however, indicate that this may vary according to dose, with higher doses of TPCP excreted in the feces. Given the structural similarity between TPCP and TMCP, it is somewhat surprising that animal studies indicate that the primary means of excreting TMCP is in the feces; as with TPCP, however, the amount excreted in the feces increased with higher doses of TMCP.[31]

The *Ortho*-Methyl Group

There is general agreement that TOCP (Figure 1) is significantly more toxic than either TMCP (Figure 2) or TPCP (Figure 3). The central and peripheral nervous systems are especially sensitive to TOCP toxicity.[32] It has been known since the 1930s that TOCP produces peripheral neuropathy in humans.[33] The peripheral neuropathy caused by exposure to TOCP is characterized by a one to three week delay in the onset of symptoms. As a result, it is referred to as

29 *See* NTP, *supra* note 7; *see also* Kurebayashi *supra* note 5.

30 *See* NTP, *supra* note 7.

31 *Id.*

32 The reproductive system is also particularly vulnerable; *see* NTP, *supra* note 7; *see also* Latendresse, *supra* note 5; *see also* WHO, *supra* note 4; *see also* Sajalendu Nanda & Pranab Kumar Tapaswi, *Biochemical, Neuropathological and Behavioral Studies in Hens Induced by Acute Exposure of Tri-ortho-cresyl Phosphate*, 82 Int'l J. Neuro. 243 (1995).

33 *See* Anthony et al., *supra* note 2; *see also* NTP, *supra* note 7.

"organophosphate-induced delayed neurotoxicity" (OPIDN) and is classified as "dying-back neuropathy."[34] TOCP has been defined as "one of the more potent OPIDN neurotoxins in humans."[35]

Several of the triaryl phosphates (including TOCP) are known to be esterase inhibitors.[36] Inhibition of neurotoxic esterase (NTE) below a critical threshold level is thought to be the biochemical lesion leading to OPIDN.[37] NTE inhibition after exposure to TOCP, which appears to be a function of dosage, presages subsequent neuropathy.[38] In terms of defining the critical threshold level, studies by Daughtrey et al. have concluded (a) that a 70% NTE inhibition level is necessary "for the induction of OPDIN in hens" following acute exposure to TOCP and (b) that "NTE inhibiting in the range of 45 to 65% is necessary to elicit neuropathic effects" following repeated exposure to TOCP.

Initial symptoms include muscle cramps and soreness as well as weakness of leg muscles. These symptoms may progress to partial paralysis of the extremities (mild cases) or to complete paralysis (severe cases). The upper extremities may not even be involved initially. However, the more severe the case, the more likely that the upper extremities will become involved and the less likely that there will be a full clinical recovery. The neurological disorder in severe cases may persist for decades.[39]

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34 *See* WHO, *supra* note 4; *see also* Marino *supra* note 5; *see also* Abou-Donia, *supra* note 19; *see also* Werner Classen et al., *Susceptibility of Various Areas of the Nervous System of Hens to TOCP-induced Delayed Neuropathy*, 17 Neurotox. 597 (1996); *see also* E.R. Kinkead et al., *The Acute Delayed Neurotoxicity Evaluation of Two Jet Engine Oil Formulations*, Nat'l Tech. Info. Service (ADA222018) (1990).

35 Marino, *supra* note 5.

36 *See* Latendresse, *supra* note 5.

37 *See* Abou-Donia, *supra* note 19; *see also* Nanda, *supra* note 32; *see also* Classen *supra* note 34; *see also* Kinkead *supra* note 34; *see also* Mushtaq A. Saleem et al., *Effect of Tri-o-cresyl Phosphate (TOCP) on Proteolytic Enzyme Activities in Mouse Liver* in vivo, 17 J. Envtl. Path. Tox. & Oncology 69 (1998); *see also* Wayne Daughtrey et al., *Subchronic Delayed Neurotoxicity Evaluation of Jet Engine Lubricants Containing Phosphorus Additives*, 32 Fund. & App. Tox. 244 (1996); *See* Martin K. Johnson, *Organophosphates and Delayed Neuropathy: Is NTE Alive and Well?* 102 Tox. & App. Pharm. 385 (1990).

38 *See* WHO, *supra* note 4; *see also* Nanda, *supra* note 32; *see also* Kinkead, *supra* note 34; *see also* Johnson, *supra* note 37.

39 *See* WHO, *supra* note 4; *see also* NTP, *supra* note 7; *see also* Abou-Donia, note 19.

The NTP Working Group addressed the delayed neurotoxicity associated with exposure to TOCP. In its final report, the Working Group noted that "the onset of delayed neurotoxicity is associated with the presence of a distal axonopathy which is most prominent in long, large diameter myelinated axons of peripheral nerves and long spinal tracts."[40] The Working Group then described the distal axonopathy/recovery process as follows: [41]

> The axonopathy begins initially as a nonterminal focal lesion resembling a transection of the axon, the portion of the severed axon distal to the site of transection then degenerates followed by degeneration of the myelin sheath surrounding the distal portion of the neuron. During the period of clinical recovery, peripheral nerve fibers regenerate relatively quickly (weeks), however recovery of long spinal tracts occurs much more slowly or not at all.

In essence, axonal degeneration ("giant axonal swelling" according to Abou-Donia et al.) and "subsequent degeneration of the myelin in the most distal portion of large diameter, long axons in the peripheral and in the spinal cord motor and sensory tracts" result from exposure to the metabolite saligenin cyclic *ortho*-totyl phosphate, the active neurotoxic agent.[42] Regarding metabolism of TCP, this metabolite is produced only when an *ortho*-methyl group is present.[43]

With regard to the ten TCP isomers, TOCP contains three *ortho*-methyl groups. Such groups are not contained in either TMCP or TPCP. This explains why "[o]nly tricresyl phosphates in which at least one of the cresol residues is an *ortho*-isomer are neurotoxic; triesters which contain only *meta*- or *para*- isomers (or both) are not neurotoxic."[44] In essence, when TCP is synthesized with *para*-cresol or *meta*-cresol, it is not neurotoxic.[45]

40 NTP, *supra* note 7.

41 *Id.* (internal citations omitted).

42 *See* WHO, *supra* note 4; *see also* Nanda, *supra* note 32.

43 The nomenclature on this point is inconsistent. Abou-Donia *et al.*, note 19, refer to the required presence of an *ortho-methyl* group. Marino, note 5, indicates that this is the correct reference. However, the NTP Working Group, note 7, refers to the required presence of either *ortho-cresol* or of an *ortho-isomer* and the WHO Working Group, note 4, refers to the required presence of an *ortho-totyl* group.

44 NTP, *supra* note 7.

45 *See* Kurebayashi, *supra* note 5.

Discussion

The metabolic process described in the preceding section "could occur whenever one of the cresol groups esterified to phosphoric acid was *ortho*-cresol."[46] In fact, animal studies indicate that "preparations in which *ortho*-cresol was present predominantly as a mono-ester, with the remaining two positions being occupied by *meta*- and/or *para*-cresol, were more neurotoxic to chickens than preparations containing predominantly tri-*ortho*-cresyl phosphate."[47] Furthermore, "preparations composed of *ortho*-cresol containing mixed triesters exhibit toxicity similar to that usually associated with tri-*ortho*-cresyl phosphate."[48] The WHO Working Group reached the same conclusion, noting that mixed *ortho*-cresyl esters "are also toxic and contribute to the neurotoxic action."[49]

Of the ten TCP isomers, six contain *ortho*-methyl groups: TOCP (Figure 1), di-*ortho*-cresyl-*meta*-cresyl phosphate (Figure 4), di-*ortho*-cresyl-*para*-cresyl phosphate (Figure 5), di-*meta*-cresyl-*ortho*-cresyl phosphate (Figure 6), di-*para*-cresyl-*ortho*-cresyl phosphate (Figure 8) and *ortho*-cresyl-*meta*-cresyl-*para*-cresyl phosphate (Figure 10). The neurotoxicity of only one of these isomers (TOCP) has been addressed in depth. Further, the NTP Working Group noted that the potential neurotoxicity of long-term, low-dose occupational exposure to industrial products containing TCP has not been investigated in a comprehensive manner. However, the Daughtrey et al. and Kinkead et al. addressed the neurotoxic effects of long-term, low-dose exposure to jet engine lubricants containing TOCP. Such effects were not observed in either study.[50]

Based on the presence of the *ortho*-methyl groups, it may be presumed that six of the ten TCP isomers are neurotoxicants. Furthermore, if the NTP Working Group is correct regarding the neurotoxicity of preparations containing a single *ortho*-methyl group, then three of the isomers (di-*meta*-cresyl-*ortho*-cresyl phosphate, di-*para*-cresyl-*ortho*-cresyl phosphate and *ortho*-cresyl-*meta*-cresyl-

46 NTP, *supra* note 7.

47 *Id.*

48 *Id.*

49 *See* WHO, *supra* note 4.

50 *See* Kinkead, *supra* note 34; *see also* Daughtrey, *supra* note 37.

para-cresyl phosphate) may be presumed to be more neurotoxic than TOCP. Additional studies are required, however, to prove the validity of these presumptions.

Such studies may be mandated in part by the fact that analysis of substances for the presence of TOCP may not reveal the presence of other *ortho*-methyl groups.[51] As a result, substances containing TCP made from natural cresol isomers may contain as many as six neurotoxicants, five of which may not be detected by tests intended to detect the presence of the known neurotoxicant, TOCP.

Conclusions

Could the "Jake Walk Blues" reoccur? While such a massive poisoning is unlikely, it is not impossible. Instead of a contaminated product, however, a more likely scenario would be for such a situation to reoccur based on an ongoing exposure to low doses of toxicants. For example, in what may be characterized as a "good news/bad news" study, Daughtrey et al. noted that long-term, low-dose exposure to jet engine lubricants containing TCP did not produce OPIDN but did result in NTE inhibition. Apparently the NTE inhibition (23% - 34%) did not reach the threshold necessary to result in OPIDN (70%) or to elicit neuropathic effects (45%-65%).[52] The long-term effects of NTE inhibition were not addressed.

Given the wide range of uses of TCP, the fact that TCP made from natural cresol isomers may contain as many as six isomers that are (or appear to be) neurotoxicants and the fact that very little is known about five of the six isomers, industry in North American may wish to follow the lead of the Japanese. Since 1971, the Japanese have manufactured TCP utilizing only synthetic cresol isomers.[53] Because the synthetic isomers do not contain the unwanted components that are present in natural cresol isomers, the TCP produced using synthetic cresol isomers does not contain the ten isomers discussed herein. This approach has not been adopted in North America, apparently because synthetic cresol isomers are more expensive than natural cresol isomers.[54]

51 *See* NTP, *supra* note 7.

52 *See* Daughtrey, *supra* note 37.

53 *See* WHO, *supra* note 4.

54 *See* NTP, *supra* note 7.

The WHO Working Group noted that individual variability made it impossible to establish a safe level of exposure to TOCP. It may be presumed that such individual variability may exist with regard to the other five TCP isomers that also appear to be neurotoxicants. Consequently, it may be in the best interests of both the public and those firms that manufacture TCP utilizing natural cresol isomers to convert to the use of synthetic cresol isomers. The costs of not doing so, especially if low levels of exposure over long periods of time result in significant neurological or reproductive injury, may be politically, legally and economically unacceptable.