

# Mobil

**AN ASSESSMENT OF THE RISKS  
OF DELAYED NEUROTOXICITY  
FROM INDUSTRIAL AND COMMERCIAL USES OF  
TRICRESYL PHOSPHATE**

**PROJECT STATUS REPORT  
MTR-21-6S-90**

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July 9, 1990

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**RISK ASSESSMENT:**  
**NEUROTOXICITY OF TCP**

Under the auspices of the ad hoc Committee for Tricresyl Phosphate, we prepared a document entitled "An Assessment of the Risks of Delayed Neurotoxicity from Industrial and Commercial Uses of Tricresyl Phosphate". This document provides a broad view of the information necessary to formulate policy recommendations for the use of TCP in Mobil products. The document was approved by the ad hoc Committee, and forwarded to its parent Safety and Health Committee on July 3, 1990.

We suggest that the Assessment be issued as a project status report from MEHSL. In this form it can be catalogued and placed in the Archive, and thus become permanently available as a Mobil document. It will be a useful reference, and may find utility in Marketing as a means for explaining Mobil policies concerning this oil additive.

  
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/ddw  
PHC0709

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## Summary

Assessment of the risks of neurotoxicity incurred from the presence of tricresyl phosphate (TCP) and other neurotoxic aryl phosphate esters in Mobil products reveals two distinct classes of jeopardy: 1) risks from repeated exposures, mainly by skin contact or inhalation, incurred during manufacture, transport, use or disposal of products; and 2) risks from ingestion exposures due to diversion of a product (or discarded containers of a product) such that food or beverages become contaminated. History of a century of use of aryl phosphate esters reveals that risks of the first class are minimal, but that risks of the second are significant.

Estimation of the doses acquired in a variety of typical workplace exposure scenarios reveals that a non-toxic dose is likely to be exceeded only in operations involving undiluted aryl phosphate ester. Formulations containing less than 1% TCP incur virtually no risk in industrial or commercial operations.

For exposure standard, which applies only to tri-*ortho*-cresyl phosphate.

In the last century as many as 60,000 people have suffered delayed neurotoxicity as a result of contamination of their food or water by industrial products containing aryl phosphate esters, mainly TCP. Poisoning has resulted from oil formulations containing as little as 3% aryl phosphate ester. The episodes have occurred worldwide and under a wide variety of circumstances, both intentional and accidental. Assessment of the circumstances leads to the inevitable conclusion that these events are random and unpredictable. Mitigation may be possible, but such events constitute fundamentally uncontrollable risk. Although the probability is small, the possibility of a future event of high consequence is very real.

## Introduction

Aryl phosphate esters constitute one of the better known classes of neurotoxic chemicals. A number of such compounds inhibit acetylcholine esterase (ACE), and high doses may produce acute effects by this mechanism. A more serious intoxication can result from the binding of certain aryl phosphate esters to a different "neurotoxic" esterase (NTE) in the central nervous system, which may initiate a complex chain of events culminating in delayed tissue damage in the brain, spinal cord and peripheral nerves. More than 60,000 people are believed to have suffered neurotoxic effects of this kind due to inadvertent or intentional contamination of foodstuffs or beverages with aryl phosphate esters, mostly the isomers and congeners of tricresyl phosphate. The risk of delayed neurotoxicity due to tricresyl phosphate is the specific focus of this analysis, although the general conclusions apply to other neurotoxic aryl phosphate esters as well.

## The Nature of Tricresyl Phosphate

The term tricresyl phosphate (TCP) is widely used for commercial products consisting of substantial quantities of one or more tricresyl phosphate isomers and congeners. Most commonly, TCP is made by reacting phosphorus oxychloride with a mixture of alkyl-substituted phenols derived from coal tar or petroleum. Cresols tend to predominate in the phenolic mixture, but xlenols and ethylphenols are usually present as well. Thus, the chemical composition of the final TCP product depends not only on the composition of the phenolic reactant but also upon processing specifications. With few exceptions TCPs are heterogeneous, in the molecular sense.

For many years, it was believed that the tri-*ortho* isomer of TCP was primarily responsible for its neurotoxic effects. It is now clear that many other aryl phosphate esters are active as well. It is for this reason that most tricresyl phosphates are considered to have neurotoxic properties, although the exact chemical composition of one may be very different than that of another. It is also true, however, that the potency of TCPs may vary and that certain carefully synthesized TCP products may not be neurotoxic at all. For the purpose of this document, the term tricresyl phosphate and its acronym will designate neurotoxic mixtures.



## **General Approach**

A modern risk assessment 1) identifies hazard(s), 2) describes exposure levels, 3) establishes dose response relationships, and 4) characterizes risk. Ideally, the last step results in an estimate or estimates of the probability of harm to exposed individuals, under given circumstances. (National Research Council 1983) In the present case, as in many occupational settings, it is possible to follow these procedures only in general terms. In particular, little detail is known of the frequency, intensity, or duration of exposure to aryl phosphate esters in the workplace. Inadequate data are available to support an evaluation of the probability of neurotoxicity as a function of repetitive exposure in a large human population. Fortunately, much is known of the toxicity of aryl phosphate esters, and we have many years of experience with their use in commerce and industry. It is possible to specify the toxicity of a range of dose levels in man and to compare with that range the quantities of TCP that might be absorbed in typical or worst-case situations. In this way, the seriousness of the risks can be assessed, and conclusions can be compared to the long history of the use of aryl phosphate esters in the workplace.

## **The Neurotoxicity of Tricresyl Phosphate in Man**

Tricresyl phosphate is readily absorbed after ingestion. It is also well established that TCP is absorbed through the skin of both man and experimental animals. Little is known of the retention, metabolism, distribution or toxicity of aryl phosphate esters after inhalation of mists or vapors, but it is reasonable to assume that the hazard exists by this route as well.

The nature of the hazard of TCP was first recognized from cases of human intoxication. However, most of what is known of the toxicology and mechanisms of organophosphorus-induced delayed neurotoxicity comes from the study of experimental animals. It is the purpose of this analysis to review available information, clinical and experimental, in order to evaluate the potential human toxicity of TCP as it appears in Mobil products. Risks of delayed neurotoxicity will be examined under two general categories: exposures in industrial and commercial operations, and exposure from contamination of foodstuffs or beverages.

Tricresyl phosphate and its congeners are known both from human poisoning episodes and from studies of experimental animal models to be acutely toxic and also cumulative in action. After absorption, toxic esters are metabolized, and the metabolite binds to an enzyme in the central nervous system. If a sufficient quantity of the enzyme (approximately 70%) is organophosphorylated, subsequent molecular changes in the bound complex produce a degradation of nerve structure, delayed neurotoxicity (Lotti and Johnson 1980, Johnson 1981). If less than the threshold fraction of enzyme is bound, no neurotoxicity results and new enzyme is generated (Johnson 1974). It is by this mechanism that repetitive small and otherwise non-neurotoxic doses may or may not exert a cumulative effect.

For these reasons, it is necessary to discriminate between the adverse effects of sequential exposures such as might occur in an occupational environment, and the possible toxicity of a single dose received in an exposure episode not repeated within a specific period of time. For this purpose, the period of time is 60 days. (Appendix A)

To determine the levels shown in Table 1, the principle of virtual certainty was employed. For example, after literature review and consideration of all available data, it is regarded as a virtual certainty that the Estimated Non-toxic Repeat Dose (ENRD) is equal to or less than 14 mg/day in a 70 kg man. Similarly, it is regarded as a virtual certainty that a dose of 3 g or more, the Estimated Toxic Single Dose (ETSD), would produce neurotoxicity in at least a few 70 kg individuals if given to a large human population. Defined in this way, the levels delimit three dosage regions: a "safe" zone, a zone of clear danger, and a range of uncertainty between. The levels and zones are intended as benchmarks against which to judge estimated quantities of absorbed toxicant in specified situations. (Details in Appendix A)



**Table 1**  
**Non-Toxic and Toxic Doses of TCP**

	<b>Estimated Non-Toxic Dose of TCP*</b>	<b>Estimated Toxic Dose of TCP*</b>
<b>Single Dose**</b>	70 mg or less 1.0 mg/kg (ENSD)	3 g or more 43 mg/kg (ETSD)
<b>Repeated Doses</b>	14 mg/day or less 0.2 mg/kg/day (ENRD)	1.4 g/day or more 20 mg/kg/day (ETRD)

\* - Levels based on 70 kg individual

\*\* - Within a 60 day period

See Appendices A and B for the basis of the estimates

### **Exposures in the Industrial/Commercial Environment**

Tricresyl phosphate has been used in commerce and industry for more than 60 years. During that period there have been remarkably few reports of neurotoxicity resulting from industrial uses, although hygiene and personal protective practices have not always been ideal. (Appendix C).

Aryl phosphate esters become a risk only when and to the degree that individuals are exposed to the chemical, and absorb it. The two major routes of exposure in the workplace are dermal contact, and inhalation of mists and vapors. Because the vapor pressure of aryl phosphate esters is very low, they do not appear in quantity in the atmosphere as vapor. However, they may occur as mists, either in pure form or as a component of petroleum-based lubricants. In poorly regulated workplaces, oral ingestion might occur via transfer of the chemical from hands, utensils or other objects.

### *Evaluation of the Dose Absorbed from Dermal Contact*

The flux rate of aryl phosphate ester through human skin has been evaluated based upon a radiolabeled tracer study in human subjects and experimental animals (Hodge and Sterner 1943; Appendix D). The flux rate, conservatively estimated, is **0.02 mg/sq cm/hour** when the skin is fully wetted with undiluted material. Although there may be vehicle effects of diluents, it is a generally reasonable assumption that the amount absorbed through the skin from a solution of aryl phosphate ester is proportional to the concentration of the ester in the solution. The calculation is as follows:

$$\text{Absorbed dose (mg)} = J (\text{flux rate in mg/cm}^2/\text{hr}) \times \text{Area (in cm}^2) \times \text{Time (in hours)} \times \text{Concentration (w/w)}$$

Table 2 shows the results of this calculation for several scenarios of exposure. In the first two, prolonged contact of the hands and forearms with pure TCP is predicted to result in absorption of quantities in excess of the Estimated Non-toxic Doses, single or repetitive (ENSD, ENRD). The third and fourth scenarios predict the quantities absorbed in circumstances where hands and forearms are in prolonged contact with an oil containing 3% aryl phosphate ester, in which a 4 hour exposure results in the absorption of 6.1 mg or less. The last scenario represents an accidental exposure in which the entire body is wetted with oil containing 3% TCP, and an hour elapses before it is removed. In such an accident, it is predicted that 11 mg would be absorbed, a quantity less than one sixth of the ENSD of 70 mg. It is to be emphasized that the calculation uses a conservatively estimated flux rate, and the actual quantities absorbed would probably be less than those in the table.

**Table 2**

#### **Estimation of the Dermal Absorbed Dose of TCP in Industrial Exposure Scenarios**

<b>Situation</b>	<b>Area (cm<sup>2</sup>)</b>	<b>Time (hours)</b>	<b>Absorbed Dose (mg)</b>
One hand wetted, pure TCP	675	4	54
Hands and forearms wetted, pure TCP	2550	4	204
One hand wetted, 3% solution in oil	675	4	1.6
Hands and forearms wetted, 3% solution	2550	4	6.1
Entire body wetted, 3% solution	1.85x10 <sup>4</sup>	1	11

A typical average ventilation rate for a 70 kg male worker for 8 hours is 20 liters/minute, 1.2 m<sup>3</sup>/hour or ~10 m<sup>3</sup> in an 8 hour workshift.

**Table 4**

**Inhaled Dose of Aryl Phosphate Esters  
at Maximum Permissible Oil Mist Concentrations  
(8 Hour Workshift)**

<b>Atmospheric Contaminant</b>	<b>C<sub>o</sub></b>	<b>C<sub>e</sub></b>	<b>V</b>	<b>D</b>	<b>Amount Inhaled (mg)</b>
<b>T-o -CP</b>	0.1	1	1.2	8	1.0
<b>Oil Mist with 1%TCP</b>	5	0.01	1.2	8	0.5
<b>Oil Mist with 3%TCP</b>	5	0.03	1.2	8	1.4

Granting the assumptions above (page 8) these quantities of inhaled ester may be compared with the ENRD of 14 mg of TCP. Although pure T-o -CP is a more potent neurotoxin than the TCP mixture of isomers and congeners, the standard is protective when the atmospheric component is pure T-o -CP.

*Evaluation of the Amount Ingested in the Workplace Environment*

In well-regulated commerce and industry, there is little or no potential for ingestion of neurotoxic aryl phosphate esters in the workplace.

Under less than satisfactory conditions, absorption by the oral route may occur by hand-to-mouth transfer of toxicant, inadvertant transfer to foods or utensils, or from swallowing inhaled mist droplets returned by the mucociliary apparatus of the upper air passages. Although quantitation is difficult, it is considered unlikely that more than a few milligrams might be ingested by transfer from a contaminated workplace environment, without a serious breach of hygiene standards. Innapropriate or mislabeled containers are known to have resulted in inadvertant ingestion, and neurotoxicity. Although the possibility of ingestion clearly exists, history confirms that the risks of workplace intoxication by this means, even in less than ideal circumstances, are negligible (Appendix C).

### **Exposure From Contamination of Foodstuffs or Beverages**

More than 60,000 people are believed to have suffered from the neurotoxic effects of aryl phosphate esters, virtually all of them from contamination of foodstuffs or beverages (Metcalf, 1982). Perhaps the most infamous episode in the United States occurred in 1930 and 1931 after TCP had been used in the illicit concoction of a "ginger extract" which was consumed during Prohibition by certain individuals because of its high ethyl alcohol content. Neither the formulator of the extract nor the manufacturer of the TCP apparently knew of the neurotoxicity of aryl phosphate esters. As many as 50,000 people may have suffered neurological damage from drinking the ginger extract, many with symptoms which persisted throughout their lives (Smith 1930, Morgan 1982). Another 10,000 cases occurred in Morocco in 1957, when a lubricating oil containing 3% TCP was mixed with olive oil and sold for cooking purposes. The most recent event occurred in 1986 when a 4 year old Canadian child drank one swallow of pure TCP, a pump lubricant stored in a 12 oz. ale bottle (Goldstein 1988). Known poisoning episodes are tabulated in Appendix E, and demonstrate that the problem has been worldwide, and that the modes of contamination include a wide variety of intentional and unintentional situations.

Utilizing the standards for human toxicity given in Table 1, it is possible to predict the volumes of generic products which may cause, or not cause, neurotoxicity from ingestion, Table 5.

Table 5

**Estimated Non-toxic and Toxic Oral Doses  
of TCP-containing Products  
in a 70 kg Individual**

	Pure TCP (ml)	1% TCP* in Oil (ml)	3% TCP* in Oil (ml)
Estimated Non-toxic Single Dose	0.06	7.8	2.6
Estimated Non-toxic Repeat Dose	0.01/day	1.6/day	0.5/day
Estimated Toxic Single Dose	2.6	333	111
Estimated Toxic Repeat Dose	1.2/day	156/day	52/day
Specific Gravity (~)	1.15	0.9	0.9
TCP Concentration (mg/ml)	1150	9	27

\* - % = w/w

Since risks are clearly associated with the oral ingestion of aryl phosphate esters, is there a concentration of ester dissolved in oil which would be regarded as non-hazardous under all circumstances? Although the potency of the particular mixture of esters would be a consideration, an estimated maximum daily intake (EMDI) of food-grade oil and the ENRD could be used to define such a standard. For this purpose 100 g of oil (~110 ml, 3.75 fluid ounces) is regarded as a virtually-certain EMDI. That volume of an otherwise innocuous oil containing 14 mg of TCP, ingested once daily, is predicted to be harmless in a 70 kg individual. Thus, a non-hazardous oil would have a TCP concentration of not more than 0.014g/100g, or approximately 0.013% w/v.



## Characterization of the Risk

The major hazardous property of certain aryl phosphate esters is their ability to produce delayed neurotoxicity. History suggests and dose calculations confirm that the workers' risk of delayed neurotoxicity in commercial and industrial applications of TCP and other aryl phosphate esters can be regarded as *de minimis*.

When exposed by the dermal route, prolonged contamination of much of the body surface with pure TCP is requisite to the absorption of a clearly toxic dose. Products containing TCP as an additive represent a risk in relation to the concentration of neurotoxic aryl phosphate esters in the product. Oils containing 3% or less of TCP are predicted to constitute no threat to workers, given even partial adherence to exposure standards and workplace protective procedures. In a scenario simulating accidental contamination of the entire body surface with an oil containing 3% TCP, a 6 hour contact time would not result in the absorption of more than an estimated non-toxic single dose (ENSD).

Worker exposure to TCP via the inhalation of mists and vapors is a hazard and a potential source of risk. From both the historical and the experimental standpoint, the risks from inhalation appear to be minimal. However, TCP consists of a mixture of isomers and congeners, and many of the congeners are now known to induce delayed neurotoxicity (Mobil 8e Notification to the USEPA 1990, Johnson 1975, Bondy et al. 1960). This calls into question the adequacy of a workplace exposure standard which relies only upon evaluation of the concentration of the tri-*ortho*- isomer of TCP in the atmosphere (ACGIH 1989). The standard, also promulgated by OSHA and the EC, has been based on the presumption that the tri-*ortho*- isomer was primarily responsible for the neurotoxic properties of TCP. Current product specifications for TCP in which the T-*o* -CP content is limited to 1% or less are based upon the same presumption.

Assuming the presence in the atmosphere of an undiluted mixture of TCP esters containing 1% T-*o* -CP, an airborne concentration of 1.5 mg/m<sup>3</sup> of the mixture would result in an 8-hour inhaled dose of 14 mg of TCP, the ENRD. Although it is unlikely that such a level would be tolerated in modern industrial operations, even higher concentrations of TCP would not be prohibited under the current standard.



When an oil contains 3% or less of TCP, adherence to the occupational standard for mineral oil mists limits the inhaled dose to approximately 1.4 mg or less in an 8 hour period. This value compares favorably with the non-toxic dose (ENRD) of 14 mg/day, for a 70 kg individual.

In the well-regulated workplace, ingestion exposure to aryl phosphate esters does not occur. Even in substandard conditions exposure by ingestion, well known as a serious problem in other circumstances, does not appear to constitute a significant source of risk.

In the last century as many as 60,000 people have suffered delayed neurotoxicity as a result of contamination of their food or water by industrial products containing aryl phosphate esters, mainly TCP. Poisoning has resulted from oil formulations containing as little as 3% aryl phosphate ester. The episodes have occurred worldwide and under a wide variety of circumstances, both intentional and accidental. Assessment of the circumstances leads to the inevitable conclusion that these events are random and unpredictable. Mitigation may be possible, but such events constitute fundamentally uncontrollable risk. Although the probability is small, the possibility of a future event of high consequence is very real.

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## **TCP Risk Assessment Appendix A**

### **Determination of Estimated Toxicity Levels of Tricresyl Phosphate in Man**

The vast majority of known human cases of aryl phosphate ester intoxication have resulted from ingestion of contaminated food or beverages. That notwithstanding, there are no exact determinations of the doses of TCP that have produced the toxic effects in man. It is well established in the world literature that the domestic fowl provides a useful and predictive experimental model of aryl phosphate ester intoxication in man. (Johannsen 1977). Almost all of the data derived from this model over the last sixty years have been based upon oral administration of the toxicant. The following consideration, therefore, is based upon oral exposure data.

In the occupational environment oral exposure is of little consequence, given even rudimentary standards of industrial and personal hygiene. The standards tabulated below are intended for use in the occupational environment. For this exercise, it is a general assumption that absorption of aryl phosphate esters by either the pulmonary or dermal routes would produce no greater toxic manifestations than the same dose absorbed via the GI tract. Long experience with industrial and commercial applications of aryl phosphate esters (Appendix C) indicates that this a reasonable assumption.

## Appendix A

### Estimated Non-toxic Single Dose Rate (ENSD) in Man

Dudek (1979) at the University of Michigan showed that 20 mg/kg or less, single dose of T-o-CP in the hen, produced brain NTE inhibition levels of less than 40%. Single dose rates of 62.5 mg/kg or more produce ataxia and NTE inhibition of more than 70%. (Dudek 1979, Calabrese and Bursian 1984) The dose rate of 20 mg/kg is taken as a virtually-certain safe dose in the hen.

#### Assumptions:

1. Oral bioavailability in men and hens is the same.
2. Doses scale linearly with body weight between hens and men, with a comparative sensitivity factor.
3. TOCP is not less than 2.5 times as toxic as TCP.
4. It is regarded as a virtual certainty that man is not more than 5 times as sensitive to the effects of aryl phosphate esters as is the hen. In order to account for individual sensitivity variations in man, an additional factor of 10 is appropriate. Thus, a safety factor of 50 is incorporated in the following calculation.

$$\text{ENSD}_{\text{man}} = \frac{20 \text{ (mg/kg)} * 2.5 \text{ (TOCP} \rightarrow \text{TCP)} * 70 \text{ (kg)}}{50 \text{ (SF)}} =$$

70 mg or less, 70 kg man

### Estimated Non-toxic Repeated Dose Rate (ENRD) in Man

In the hen, the virtually-certain non-toxic repetitive dose rate is 10 mg/kg/day, based on a study (Huntingdon Research Center 1990) in which that rate was administered orally once daily, five times weekly for ten consecutive weeks. Although data from other studies suggest that the value might be greater, this datum is chosen because it is based on a prolonged duration of administration.

## Appendix A

### Assumptions:

1. Oral bioavailability in men and hens is the same.
2. Doses scale linearly with body weight between hens and men, with a comparative sensitivity factor.
3. A safety factor of 50 is incorporated in the calculation, to account for greater sensitivity of the human in relation to the hen, and for variation of individual sensitivity in the human population.

$$\text{ENRD}_{\text{man}} = \frac{10 \text{ (mg/kg/day)} * 70 \text{ (kg)}}{50 \text{ (SF)}} = 14 \text{ mg/day or less, 70 kg man}$$

### Estimated Toxic Single Dose (ETSD) in Man

Smith (1930) observed that as little as one ounce of contaminated Jamaica Ginger Extract was sufficient to produce neurologic deficit. We have estimated that the Extract contained approximately 3.3 grams of TCP per fluid ounce (Appendix B). On this basis, we conclude that

$$\text{ETSD} = 3 \text{ g or more, 70 kg man}$$

This value, corresponding to a dose rate of ~40 mg/kg, is consistent with the conclusions of others (Metcalf 1982).



## Appendix A

### Estimated Toxic Repeated Dose (ETRD) in Man

In a study of hens administered TCP once daily, 5 days per week for 10 weeks (HRC, 1990), a dose rate of 60 mg/kg/day produced ataxia in 19/30 hens and an average NTE inhibition of 70%. In the same study, 20 mg/kg/day produced neither ataxia nor central nervous system lesions, and an average NTE inhibition of 43%. The minimally toxic repeat dose in the hen, to a virtual certainty, is taken to be 40 mg/kg/day.

#### Assumptions:

1. Oral bioavailability in men and hens is the same.
2. Doses scale linearly with body weight between hens and men, with a comparative sensitivity factor.
3. The best estimate of the comparative sensitivity of man in comparison to the hen to the delayed neurotoxic effects of aryl phosphate esters is a factor of 2. For this purpose, additional safety factors are not employed because they would reduce the certainty of the estimate.

$$\text{ETRD}_{\text{man}} = \frac{40 \text{ (mg/kg/day)} * 70 \text{ (kg)}}{2 \text{ (Hen} \rightarrow \text{Man)}} = 1.4 \text{ g/day or more, 70 kg man}$$

### Exposure by Inhalation

#### Appendix A

Siegel et al. (1965) have reported the results of intermittent and continuous mist exposures in experimental animals, using a mixture containing tricresyl phosphates, trixylenyl phosphates, and other trialkylphenyl esters. The TOCP concentration in the test material was less than 1.5%, the Navy specification current at the time. Oral dosage with the mixture for 5 days produced typical neurotoxicity in hens. After "continuous" exposure (approximately 23 hours per day) for 60 days, hens became neurotoxic at atmospheric concentrations of 23 mg/m<sup>3</sup> or more. At a concentration of approximately 100 mg/m<sup>3</sup>, hens became neurotoxic after 22 days. Continuous exposure for 108 days at 4.4 mg/m<sup>3</sup> or less did not produce neurotoxicity in the hen. In the "intermittent" regimen (8 hours/day, 5 days/week, for 30 days), neurotoxicity developed in hens at 50 mg/m<sup>3</sup> but not at 25 mg/m<sup>3</sup>.

It is not possible to evaluate the absorbed doses in Siegel's experiments. In continuous whole body mist exposures the test material is absorbed not only by the inhalation route but also by dermal absorption, and by ingestion through preening and contamination of food and water supplies. The experiments leave no doubt, however that 1) toxicity may occur through whole body exposure to mists, and 2) very high concentrations for prolonged periods are required. The current occupational standard (ACGIH 1988) for airborne T-o -CP is  $0.1 \text{ mg/m}^3$ , 8 hour time-weighted average, a value which is approximately 1/50th the continuous exposure no-effect level for TCP cited above.

### **Regeneration of Esterase Activity after NTE Binding**

The mechanism of organophosphorus-induced delayed neurotoxicity involves the binding of a metabolite of the toxic ester, probably substituted saligenin phosphate, to "neurotoxic target esterase" (NTE) in the brain and spinal cord. Approximately 70% of the available enzyme must be bound before neurotoxicity develops. (Lotti and Johnson 1980)

Although the function of NTE is not known, new enzyme is synthesized after inactivation by organophosphorylation. The rate has been estimated to be first order, with a half-time of 4-5 days (Johnson 1974). On this basis, it is conservatively estimated that complete regeneration would require ten half-times, or approximately 60 days. It is this interval which is cited, page 5, as a standard for discriminating between single and repetitive dose regimens.

Appendix A

### **Comparative Sensitivity of Hen and Man**

Assignment of an exact comparative sensitivity factor for man in relation to the hen depends upon reliable dose-response data in each species, a kind of data which do not exist for man. In only a few of the human poisoning episodes have there been even rough estimates of ingested dose. A satisfactory profile of molecular constituents of the toxic aryl phosphate is not available for any of the episodes. The requirement for such a profile has been documented by Bondy et al. (1960) and Johnson (1975).

Smith's observation (1930) that neurotoxicity was produced by "... as little as 1 ounce of the ginger..." was based upon "Apparently reliable histories ..." Considering that the Extract may have contained approximately 3300 mg of TCP per fluid ounce (Appendix B), this is a dose rate of about 40 mg/kg in a 70 kg individual, approximately two-thirds of the minimum neurotoxic single dose rate in the hen (Dudek 1979). The case report by Goldstein in an 18 kg child who ingested "... approximately 5-10 ml" of TCP implies a dose rate of 300 - 600 mg/kg. The child had recovered 5 weeks after the ingestion occurred.

On the other hand, Hodge and Sterner (1943) cite a 1941 Swiss paper which alleges that 150 mg of T-o-CP in cheesecake produced clinical neurotoxicity, a dose rate of approximately 2 mg/kg. Taken at face value, this estimate would suggest that man is 30 times as sensitive as the hen. In our view, fifty years of human exposures attendant to industrial and commercial applications of other esters as toxic as T-o-CP suggests that the Swiss cheesecake minimum dose level may have been underestimated.

In the absence of adequate data to support the determination of even one circumstance- and substance-specific sensitivity factor, the authors have estimated a best-guess general value to be man:hen = 2. Recognizing that the value could be greater, we have estimated that the maximum would be man:hen = 5. These estimates have been incorporated as appropriate in equations for hen-to-man extrapolations, above.

## TCP Risk Assessment

### Appendix B

#### Estimation of the Quantity of Tricresyl Phosphate in Contaminated Jamaica Ginger Extract

The paper by Morgan (1982) describes a variety of details and circumstances surrounding the preparation of adulterated Ginger Extract by Harry Gross of Hub Products Co., Boston, in 1930. There is a good possibility that the batch or batches prepared by Gross constituted the sole source of toxic Extract. As indicated below, it is calculated that Gross produced about 2000 gallons, sufficient to make 128,000 two fluid ounce bottles. This volume is more than enough to account for the 20,000 individuals or more said to have suffered from neurotoxicity in 1930 and 1931.<sup>—</sup>

On page 1866, third column, Morgan provides a recipe in which a total of 23 pounds of ingredients was to be added to a quantity of solvent (ethyl alcohol) sufficient to make a 75% solution. (Proof of alcohol not listed, probably 160 - 180.) In this context the "quantity sufficient" direction is unusual. In the pharmaceuticals of the day this direction was usually accompanied by a volume specification in the formulation of a w/v solution, such as "to the listed ingredients add liquid, q.s. to make 1 gallon."

The text further indicates that Gross prepared the adulterated Extract by substituting Lyndol™, an oily mixture of cresyl phosphate esters, for the castor oil ingredient at a rate of 8 pounds per batch. On a weight basis,  $100 \times (8 \text{ lbs of Lyndol}) / (23 \text{ lbs of ingredients} + 69 \text{ lbs of solvent}) = 8.7\%$  Lyndol w/w in a solution which is 75% solvent by weight.

On page 1866, third column near the bottom, Morgan indicates that 135 gallons of Lyndol™ were shipped to Gross, a quantity Morgan calculated to be sufficient to prepare 640,000 2 fl ounce bottles. On a volume basis, this represents a total of 135 gallons of Lyndol in 10,000 gallons of Extract, 1.35% v/v. This concentration is not consistent with the w/w value above.

## Appendix B

On page 1865, column 1, a typical specification in w/v for "Fluid Extract of Jamaica Ginger - USP" is listed as 5 grains per cm<sup>3</sup>, convertible to 324 mg/ml, total solids per unit volume. Under this specification, 23 lbs of listed ingredients would be diluted to a total volume of 8.5 gallons, and the Lyndol content would have been 0.94 lbs/gallon (3.33 grams per fluid ounce) on a weight per volume basis.

It seems likely that this USP specification was the target for the formulator of adulterated Jamaica Ginger Extract. If this was the case, each 2 ounce bottle of Jamaica Ginger Extract would have contained approximately 6.7 g of cresyl phosphate ester, a dose rate of approximately 95 mg/kg mixed isomers in a 70 kg man.

If one assumes the specific gravity of the Extract to be 1.2 and a Lyndol content of 8.7% w/w (second paragraph, above), then the calculated content in a 2 oz bottle would have been  $(1.2 * 60 \text{ ml}) * 0.087 = 6.2 \text{ g}$ . This would appear to be in reasonable agreement with the results of the USP calculation.

Another paper (Metcalf, 1982) lists without citation an approximate concentration of 2.5% T-o -CP in the toxic Ginger Extract. This is consistent with the above if Lyndol contained about 23% T-o -CP, a reasonable estimate. This would have resulted in a dose of 1.5 g and a dose rate of approximately 22 mg/kg tri-ortho-cresyl phosphate in a 70 kg man, from each 2 oz bottle of Extract.

It is concluded that the Jamaica Ginger Extract prepared by Harry Gross contained, per ml of Extract, approximately 110 mg Lyndol and 25 mg T-O -CP. Dose rates in a 70 kg man from a 2 ounce bottle of adulterated Extract are estimated to have been 95 mg/kg mixed TCP isomers, and 22 mg/kg T-O -CP. It is not known how often or what total quantity of the Extract may have been consumed by those who were injured by the neurotoxic adulterant, although Smith (1930) indicates that neurotoxicity occurred after ingestion of one half of a 2 ounce bottle.

It also seems likely that Morgan was confused when he calculated that 135 gallons of Lyndol would have been diluted to 640,000 2 oz bottles. At the "USP" concentration of 3.33 grams per fluid ounce, 135 gallons of Lyndol (sp gr = 1.18) would have been diluted to ~ 1400 gallons of Extract or ~ 91,000 2-oz bottles.



## TCP Risk Assessment

### Appendix C

#### Experience with the Use of Aryl Phosphate Esters in the Industrial Environment

There are only a few reports of neurotoxicity resulting from legitimate manufacture, transport, use or disposal of aryl phosphate esters in commerce and industry.

Hunter (1944) describes three cases in Britain during WW II, in which synthesis of TCP and other aryl phosphate esters took place in open vessels and in a tightly enclosed environment. In later simulations atmospheric concentrations in the plant were measured at 0.55 - 1.66 mg/m<sup>3</sup>; there was no mention of dermal contact, although this seems a likely eventuality. All three cases had severe neurologic abnormalities, but experienced extensive if not complete recovery.

Inoue (1988) cites two additional cases in German chemical plants (1943, 1946) but gives no details.

Bidstrup and Bonnel (1954) describe a workman who became permanently impaired after employment in a pesticide manufacturing operation, and exposure to reactants containing TCP and TOCP. The route(s) by which the toxic dose were acquired were not established.

In his historical review, Metcalf (1982) cites without reference a 1959 incident in which "...a number of workers in an East German plastics factory were poisoned by airborne TOCP." Unfortunately no additional details were given, and no other descriptions of the incident have been found.

Mackerer (1989), in a review of the health effects of mists from metal-working fluids ("cutting oils"), listed triaryl phosphates as a common additive ingredient but did not cite a single instance of neurotoxicity resulting from mist exposure. This is not surprising, given the small quantities of airborne ester that can be inhaled from an industrial atmosphere that meets or even approximates current health standards.



Two reports summarize the results of clinical studies of small populations of workers who had substantial occupational exposure to aryl phosphate esters.

Baldrige *et al.* (1959) describe daily exposure of Navy personnel during the installation and operation of large elevator systems on the aircraft carrier *Leyte* in 1956. The elevator hydraulic fluid was a triaryl phosphate oil designated TCP-1. A total of sixteen individuals were known to be exposed; 8 unexposed workers were evaluated for comparison. In addition to routine minor exposures, there were exceptional incidents including a spill in which "Nine men were exposed on hands, arms and legs during cleaning operations, and the total duration of exposure was one to two hours, after which the exposed areas were completely cleaned with soap and water and clothes were changed." Evaluations included plasma and red cell acetylcholine esterase, neurologic exam, blood counts and general physical examinations. No adverse effects were discovered.

Tabershaw *et al.* (1957) conducted a careful evaluation of 34 workers in a plant manufacturing organic phosphates, including TCP. Of the 34, 28 were classed as having had "high exposure". Conditions in the plant were less than ideal; atmospheric concentrations of TCP ranged from 0.27 mg/m<sup>3</sup> (general air) to 3.40 mg/m<sup>3</sup> (decolorizing kettles). Evaluations included plasma acetylcholine esterase and clinical examinations. Tabershaw's conclusions were:

"It is significant, however, that with an average worker exposure of 8.9 years, only minimal clinical effects were observed which did not entail any lost time or serious medical investigation. The neuromuscular findings cannot be definitely attributed to tricresyl phosphate, and the gastrointestinal symptoms may well be due to the other chemicals used in the process. It is of further interest that, although industrial hygiene conditions were not very favorable, as exemplified by the policy of permitting workers to eat in the manufacturing areas, the clinical data are conspicuous by the absence of any serious disease attributable to tricresyl phosphate."

# **Estimation of the Rate of Dermal Absorption of TOCP in Man**

**Appendix D**

**page 26**

Reference: The Skin Absorption of Triorthocresyl Phosphate as Shown  
by Radioactive Phosphorus, Hodge and Sterner, J Pharm Exp Thera 79:225, 1943

	Subject S	Subject H	Urinary Excretion (Counts)		
			Subjects ->	24 hours	
Applied Dose (mg)	220	110	3/5, 8:30 +	S 29	H 38
			3/5, 9:30+	115	56
Counts/min/dose	869000	434500	3/5, 11:45+	587	66
			3/5, 3:45+	327	40
Area (sq cm)	130	130	3/5, 8:30+	477	162
			3/6, 12 m+	1180	157
Duration (hours)	3.5	3.5	3/6, 7:00+	47	-

	Subjects ->	S	H
Total Counts in Urine, 24 hours		2762	519
% Dose Excreted in Urine		0.318	0.119
Amount Excreted in Urine (mg)		0.699	0.131

In the dog, Hodge and Sterner's data indicate that of a total absorbed dose of 18 mg of TCP, 2.95 mg (~16%) was excreted in the urine in the first 25 hours.

Using this relationship and the amounts excreted in urine (above), it can be estimated that the human dermal absorbed dose in mg = 4.37 0.82

Estimated Percutaneous Flux Rates  
for TOCP on human palmar skin (mg/sq cm/hr) = 0.01 0.002

Note: Hodge and Sterner comment that "...human palmar skin apparently [transfers] triorthocresyl phosphate about 100 times more rapidly than dog skin." This is not the case. The flux rate for dog skin in this investigation is calculated to be 0.0024 mg/sq cm/hour, a value virtually identical to that of subject H, and 1/4 the magnitude of the flux rate observed in subject S.

Comment: The small proportion of absorbed dose in relation to applied dose suggests that the absorption rate was maximal in both individuals. This implies that the difference between S and H is not the result of different applied doses, but rather represents individual variation.

Conclusion: In human skin, the dermal flux rate of TOCP, a typical aryl phosphate ester, is conservatively estimated to be: 0.02 mg/sq cm/hour

Estimation of Dermal Absorbed Dose of TOCP in the Dog  
Based on Table 5 and text  
Hodge and Sterner, 1943

Appendix D  
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Tissue	Weight g	Counts per sample	% of dose per gram	ToCP, microgram per gram †	Estimated Organ Weights in 10.5 kg dog g	Estimated % of Dose in Whole Organs*	Estimated ToCP in Whole Organs* mg
Skin	33	8775	0.00477	99.9	n/a	0.1574	3.296
Fascia	47	497	0.00019	4.0	200	0.0379	0.794
Fat	47	393	0.00015	3.1	850	0.1275	2.670
Liver	340	5720	0.00030	6.3	340	0.1025	2.147
Blood	300	1487	0.00009	1.9	900	0.0800	1.676
Kidney	55	173	0.00006	1.2	55	0.0031	0.065
Heart	81	95	0.00002	0.4	81	0.0017	0.036
Lung	117	282	0.00004	0.9	117	0.0051	0.106
Spleen	23	14	0.00001	0.2	23	0.0003	0.005
Muscle	224	317	0.00003	0.5	3750	0.0952	1.993
Femur (Skeleton)	50	17	0.00001	0.1	2500	0.0152	0.319
Brain	69	39	0.00001	0.2	69	0.0007	0.015
Spinal Cord	5	5	0.00002	0.4	5	0.0001	0.002
Sciatic Nerve	10	6	0.00001	0.2	1.0	0.0000	0.000
<b>Totals</b>	<b>1369</b>				<b>8891</b>	<b>0.6267</b>	<b>13.12 ††</b>

Applied Dose, mg=2094  
Counts in dose=5575000  
Dog Weight, kg,=10500  
Application Area = 15 x 20 cm  
Application time=25.25 hours

\* - 25.25 hours after application of TOCP to abdominal skin

† - Values corrected from the original

	mg	% of Dose
Amount Excreted in Urine, 25 hr	2.95	0.141
Amount left in carcass, 25 hr ††	13.12 ††	0.627
Amount unaccounted (est.)	1.92	0.092
<b>Total</b>	<b>4.87</b>	<b>0.859</b>

†† This estimate is less than the actual quantity absorbed because H&S did not quantify labeled material in the bile, gut or gut contents. It is unlikely, however, that the tissue retention at 25.25 hours was greater than 15 mg, or that the total absorbed in 24 hours was greater than 18 mg (~0.9%) of applied dose. An estimate of the unaccounted quantity is added in the calculation to the left

Reference: The Skin Absorption of Triorthocresyl Phosphate as Shown  
by Radioactive Phosphorus, Hodge and Sterner, J Pharm Exp Thera 79:225, 1943

**Estimated  
Distribution of TOCP in Tissues of the Dog  
25 Hours after Dermal Application**

<b>Tissue</b>	<b>Estimated TOCP in Whole Organs* mg</b>	<b>Distribution, by percent of Body Burden</b>
Skin (Application site)	3.296	22.0
Fascia	0.794	5.3
Fat	2.670	17.8
Liver	2.147	14.3
Blood	1.676	11.2
Kidney	0.065	0.4
Heart	0.036	0.2
Lung	0.106	0.7
Spleen	0.005	0.04
Muscle	1.993	13.3
Femur (Skeleton)	0.319	2.1
Brain	0.015	0.10
Spinal Cord	0.002	0.01
Sciatic Nerve	0.000	0.00
Subtotals	13.12	87.5
Estimated Addn'l quantity	1.88	12.5
Estimated total body burden at 25.25 hours	15.00	100

\*TOCP plus labeled metabolites, expressed as TOCP

# TCP Risk Assessment

## Appendix E

Appendix E

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### Triaryl Phosphate Ester Poisoning in Humans Due to Contamination of Food or Beverages

Year	Place	No. of Cases	Neurotoxic Phosphate Ester	Vehicle	Motivation	Circumstances
1891	France	6	Phospho-creosote (1)	n/a	Deliberate	Tuberculosis therapy
1900-28	Europe	13	Phospho-creosote (1)	n/a	Deliberate	Tuberculosis therapy
1930-31	USA	20,000 - 50,000	TCP	Ginger Extract	Deliberate	Adulterated flavorant/medicament
1931	Europe	~300	TCP	Apiol Oil (2)	Deliberate	Use of oil as abortifacient
1938	S. Africa	68	TOCP	Cooking Oil	Inadvertant	Contamination of food-grade soybean oil
1940	Switzerland	80	TCP	Cooking Oil	Inadvertant	Machine gun oil in olive oil cans
1939-45	Germany	>200	TOCP	Cooking Oil	Deliberate	Machine gun oil used for cooking
1945	UK	17	TOCP	Cooking Oil	Unknown	Contamination of food-grade oils
1955	S. Africa	11	TCP or TOCP	Water	Inadvertant	Industrial containers used for water storage
1956	Japan	6	TOCP	Cooking Oil	Unknown	Unknown
1959	Morocco	~10000	TCP	Synth. + Olive oil	Deliberate	Olive oil contaminated with jet engine oil
1960	India	58	TOCP	Food	Inadvertant	Unknown
1962	India	>100	TCP	Flour	Inadvertant	Contamination with TCP
1967	Fiji	56	TOCP	Flour	Inadvertant	Contamination from TOCP in sack material
1980	Romania	12	TOCP	Liquor	Unknown	Unknown
1981	Sri Lanka	>20	TCP	Cooking Oil	Inadvertant	Cooking oil stored in contaminated containers
1986	USA	1	TCP	Pump Lubricant	Inadvertant	Ingestion by child, inappropriate container

Notes: (1) - A mixture of esters formed by the reaction of phosphoric acid and coal tar phenols, said to contain ~15% TOCP

(2) - Parsley extract containing 28 - 50% TOCP, used to induce abortion