Phosphate Ester Toxicity

History

Prompted by regulatory action (Department of Transportation) controlling the flame spread, the automotive industry has turned to phosphate ester plasticizers and phosphorous flame retardants. Questions concerning their toxicological and environmental safety have arisen. The Environmental Protection Agency (Office of Toxic Substances) has already placed aryl phosphate esters high on their priority list and have an active program under way.

The Ford Motor Co. has, on two occasions, alleged that Santicizer 140 (cresyl diphenyl phosphate) caused certain toxicological effects through skin absorption. Other phosphate ester customers (General Tire, Olin Corp., General Electric) have raised the toxicity issue.

Through the years, phosphate esters (particularly the trialkyl and alkyl aryl esters) have been considered relatively non-toxic. The literature reveals disastrous epidemiological effects of ortho cresylic phosphate esters on both humans and animals. Most of these data reveal neurotoxicity. Both TCP and Santicizer 140 cause demyelination (attack on nerve sheath) and inhibit cholinesterase activity. Our data also show no difference between cresylic acids designated as "low ortho" or "high ortho".

Because of the neurotoxicity problem, the plasticizer group, in late 1973, committed to exit from the cresylic-acid-containing phosphate esters. No tricresyl phosphate was manufactured or sold as a plasticizer in 1974. Santicizer 140 (CDP) will be

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discontinued by the end of 1975.

A similar product manufactured by FMC, Kronitex 100, isopropyl phenyl diphenyl phosphate (mixed isomers) is also neurotoxic. It is anticipated that the EPA will soon (if not already) learn of the neuro toxicity associated with Kronitex 100.

Santicizer 140

Although the acute oral toxicity (LD_{50}) of S-140 is low, the product appears to be highly toxic to fish (more toxic to fish than TCP) and does cause demyelination -- degeneration of the nerve sheath (myelin), causing neuro toxicity. Demyelination occurred with S-140 prepared from both high and low ortho cresylic acids.

Tri Cresyl Phosphate

The literature contains numerous studies (both animal and human) showing serious neuro toxicity of PCB. Most of the studies show the tri ortho cresyl phosphate isomer to cause the problems.

Tri Phenyl Phosphate

The medical department information shows TPP not to cause demyelination. At a recent meeting with the EPA, it was revealed that TPPa can cause cholinesterase inhibition under certain testing conditions.

Isopropyl Diphenyl Phosphate (Kronitex 100)

Our results show this ester to cause demyelination, results paralleling those obtained for S-140 and TCP.

FMC reportedly has published data showing Kronitex 100 not to cause neuro toxicity. The test is apparently much less stringent than

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that used for our studies.

Tertiary Butyl Phenyl Diphenyl Phosphate

Neither gross nor microscopic signs to demyelination occurred in ~~hands~~ hens treated with t-butyl phenyl diphenyl phosphate.

Nonyl Phenyl Diphenyl Phosphate

This product has displayed a low order of toxicity. The demyelination tests were negative.

Cumyl Phenyl Diphenyl Phosphate

This product has also been shown to have a low order of acute toxicity and not to cause gross demyelination.

History

As early as 1930, it was recognized that tri ortho cresyl phosphate could induce peripheral polyneuropathy in persons accidentally exposed. As a result of strict precautionary measures, cases of polyneurities or paralysis resulting from industrial or accidental exposure to TOCP have become quite rare. The neuropathogenic potential has been shown to be related to the amount of ortho cresyl isomer present. Although the tri ortho cresyl phosphate ester is the most potent neurotoxin of the group, mixed tri cresyl phosphate esters containing only a small ortho cresyl isomer content can induce neuropathy.

Results of studies demonstrate that neuropathogenic potential of various phosphate esters differ markedly.

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An outbreak of the so-called "ginger paralysis" caused by the adulteration of Jamaica ginger occurred in the U.S. in 1930. Some 10,000 North Africans were paralyzed in 1959 through the ingestion of cooking oil contaminated with TOCP. A number of problems involving smaller groups of industrial workers was also reported.

As a consequence of these epidemics, extensive studies of the specific effects of phosphate esters on animals have been made. Over-simplifying, ortho cresylic phosphate esters affect the nervous system in two ways. First, they attack the cells of the myelin which is a fatty sheath covering nerve fibers causing them to become exposed and damaged. Secondly, these esters inhibit colinesterase activity. Acetyl choline is needed to conduct electrical impulses throughout the nervous system. Cholinesterase enzyme is required to deactivate acetyl chloine immediately after impulses have been transmitted to prohibit the repetition of the message resulting in convulsions and other involuntary effects.

It is still not clear as to the exact structures which cause this toxicity. Mono and di ortho cresyl derivatives have paralyzing activity. Actually, the mono ortho cresyl ester was six times more toxic to animals than the tri ortho cresyl compound. The pure TOCP compound attacks only the peripheral nerves while the mono and di ortho cresylic esters attack the paramiddle tract. Toxicity similar to that recorded for TCP has been found with cresyl diphenyl phosphate (S-140).

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