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RE: de Ree H, et al. "Health risk assessment of exposure to tricresyl phosphates (TCPs) in aircraft: A commentary," Neurotoxicology (2014), http://dx.doi.org/10.1016/j.neuro.2014.08.011

Dear Dr. Cranmer:

The paper by de Ree et al. mischaracterizes some key components of the reported association between exposure to aviation engine oil fumes and delayed, chronic neurological illness reported by exposed crewmembers.

The authors are correct that airline crewmembers inhale oil fumes when the ventilation air that is supplied to the cabin and flight deck is contaminated with pyrolyzed oil. It is long-recognized that engine oil fumes can contaminate the ventilation supply air on aircraft (SAE, 2011; Reddall, 1955), and all aviation engine oils used on the global commercial fleet contain tricresyl phosphates (TCPs), approximately 2-6%, by weight (OHRCA-ACER, 2014). However, the authors do not mention that the oil fumes contain a mixture of neurotoxic compounds that does include, but is not limited to, TCPs. For example, one of the two TCP blends marketed for engine oils also contains trixylenyl phosphates (ICL-IP, 2011) which are recognized as neurotoxic (NLM, 2013). Further, there is some evidence that the TCP additives in an oil can react with other chemical constituents upon heating to form additional organophosphates, such as neurotoxic trimethylolpropane phosphate (TMPP) (Wright, 1996). In addition to the reported hazardous ingredients in most engine oils, chemical analyses of engine oil fumes have identified a long list of unreported compounds, such as acrolein, amines, carboxylic acids, carbon monoxide, formaldehyde, toluene, and xylene (ASHRAE, 2012; ACARM, 2007; DERA, 2001; van Netten, 2000; Paciorek, 1978). Some of these compounds may be present in the bulk oil sample, and others are generated upon heating the oil to temperatures within the range of an operating aircraft engine or auxiliary power unit. Individually, these compounds may not be recognized first and foremost as neurotoxins, but the impact on the central nervous system of inhalation exposure to the complex chemical mixture in oil fumes has received little attention.

The authors reference the potential for transient exposures to low-levels of oil-based contaminants in the ventilation air, and attempt to measure those potential exposures on a small number of flights. Certainly, there is some evidence that aircraft ventilation supply may contain low levels of oil-based contaminants on a relatively routine basis (Cranfield, 2011; Murawski and Michaelis, 2011), and on

aircraft without recognized mechanical failures sourced, at least in part, to imperfect or delayed closure of the engine seals during engine power setting changes (SAE, 2011). However, most cases of chronic neurological illness documented by airline crewmembers follow documented exposure to oil fumes in the flight deck, cabin, or both, that is significant enough to necessitate a change in flight plan (i.e., cancelled or diverted) and emergency medical care to address acute symptoms (Murawski, 2011).

The authors' claim that crews consider exposure to ToCP responsible for the delayed neurological symptoms that can follow an exposure to oil fumes is also misstated. The TCP blends marketed for aviation engine oils must contain a minimum of 99.8% meta/para isomers; thus, no more than 0.2% of the TCPs in aviation engine oils will contain some combination of as many as six ortho isomers, one of which may be ToCP (SAE, 2005). This means that the ToCP content in the oil will range from 0 – 0.006%, assuming an average 3% total TCPs. If the combined ortho isomer content of the TCPs is as low as the authors suggest (0.03 – 0.06%), then the likelihood of finding ToCP is even lower, since it means that an oil with a 3% TCP content would contain 0 - 0.0018% ToCP. Given these facts, it makes no sense to rely on ToCP, either as a metric of exposure to oil fumes on aircraft or as a stand-alone metric of neurotoxic hazard, when there is little, if any, ToCP in the fumes, and even if ToCP is present, it is not the only neurotoxic compound in the fumes.

Also on the subject of TCPs, the authors characterize the meta and para TCPs that dominate commercial engine oil formulations, as "non-toxic." This, too, is incorrect, and hinges in part on one's definition of "toxic." The authors reference a narrow (albeit widely accepted) definition of neurotoxic that is specifically tied to inhibition of neurotoxic esterase (NTE) activity, overt signs of paralysis, and spinal cord lesions. However, affected crews' rarely describe such symptoms; instead, they largely describe symptoms that imply central nervous system damage, such as deficits in speech, concentration, and information processing.

Recently published research demonstrated significant inhibition of liver acyl peptide hydrolase (APH) and carboxylesterase1 (Ces1) activity in mice that had ingested either Durad 125 (i.e., one of two blends of TCPs marketed for aviation oils) or the tri-para isomer of TCP (i.e., one of four isomers that dominate both commercial TCP blends added to aviation oils) (Baker et al., 2012). Assuming these findings apply to *inhalation exposure* to these same TCPs, they are significant because APH activity is implicated in cognition (Pancetti et al., 2007; Richards et al., 2000). Likewise, the Ces1 enzyme plays a role in the body's detoxification processes (including the lungs and central nervous system), and the inhibition of Ces1 activity has been shown to potentially impair overall immune function and the control of tumor cells/inflammatory processes (Markey, 2011). Thus, the finding that TCPs (after being bioactivated in the liver) suppress Ces1 activity may help to explain reports of immune system deficiencies, as well as reduced tolerance to subsequent exposures of toxic compounds, among affected airline crews. Ces1 activity is known to vary widely between people, influenced by genes, gene expression, and environmental factors (NCBI, 2014; Ross et al., 2012). So, it is possible that low Ces1 activity (whether naturally low or artificially depressed by a fume event) may increase a person's susceptibility to ill effects following exposure to oil fumes. Likewise, high Ces1 activity may offer some protective effect.

Finally, the authors' risk assessment does not mention emerging research on endocrine disruptors (such as TCPs) regarding the potential for non-linear dose-response relationships (Vandenberg, 2014) and clinical effects of exposure at noncytotoxic concentrations (Hausherr et al., 2014).

The authors seem open to the possibility that inhalation exposure to chemicals on aircraft may cause ill health in some cases but, in considering a toxic mechanism for crew reported neurological symptoms after exposure to oil fumes, they pose the wrong question (i.e., is their evidence of exposure to ToCP on non-incident flights sufficient to cause neurological symptoms in crewmembers who work on non-incident flights over the long term?). They find no evidence of ToCP, which is to be expected. Further, they do not reference a case-series, for example, of crewmembers who report neurological illness after working on non-incident flights, such as those sampled. Still, they conclude that, given no evidence of exposure to ToCP on the 20 flights, there is no evidence of a workplace basis for the reported neurological symptoms, either.

Sincerely,

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