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Press Release

Peviva products are for research use only

- **Toxicological profile for vinyl chloride to include mention of keratin 18 serum research biomarkers in examining hepatic effects due to exposure** (March 2, 2016)

  West Chester, OH, March, 2016 – The toxicological profile for vinyl chloride includes keratin 18 (K18; also referred to as cytokeratin [CK18]) as a potential useful research biomarker for hepatic effects due to vinyl chloride exposure. Diapharma Group, Inc. is the exclusive provider of Peviva's K18 biomarker kits (research use only) and would welcome a visit to Booth 219 during the SOT meeting in New Orleans.

  Vinyl Chloride and New Orleans - Vinyl chloride is a potent liver toxic chemical widely used in the industry and is a known human carcinogen. In fact, Louisiana has the second most number of facilities by state that produce, process, or use vinyl chloride, and it is first among states in amounts of vinyl chloride released in the air. The potential harm and significance of this was highlighted in a recent AP report in March 2012 that described an explosion and fire at a chemical plant between Baton Rouge and New Orleans that resulted in releasing of vinyl chloride into the air.

  Vinyl Chloride Exposure – Recent research studies suggest that workers exposed to vinyl chloride on a regular basis may develop liver steatosis and fibrosis. In one study, liver injuries in vinyl chloride workers, verified by liver biopsies, were reported to correlate with K18 blood concentrations (M65 ELISA), despite normal ALT and AST values (Cave *et al.*, 2010). An influence of obesity or alcohol abuse could be ruled out, leaving the toxic effect of vinyl chloride as the only reasonable cause for the liver diseases. The workers were exposed to very high levels at the time, but the effects are still real to those in Rubbertown who have died from cancer or are suffering from liver disease.

Table 1 CK18 in vinyl chloride-related TASH

Laboratory Variable	Healthy Unexposed Controls	Healthy Chemical Worker Controls	TASH
ALT (U/L)	14.0 (8.6)	28.4 (11.3)	29.0 (48.3)
AST (U/L)	20.8 (3.3)	21.5 (7.3)	19.9 (8.0)
CK-18 M30® (U/L)	164.1 (26.3)	150.9 (74.6)	183.7 (88.6)
CK-18 M65® (U/L)	215.8 (98.6)	272.7 (71.3)	**583.4 (319.2)[a,b]**

[a] $p<0.001$ *vs.* Healthy Unexposed Controls;
[b] $p<0.001$ *vs.* Healthy Chemical Worker Controls

Cave, M., Falkner, K.C., Ray, M., Joshi-Barve, S., Khan, R., Bon Homme, M., McClain, C.J. Toxicant-Associated Steatohepatitis in Vinyl Chloride Workers. *Hepatology.* 2010; 51(2):474-81

Vinyl Chloride and OSHA - If an employee is exposed to vinyl chloride at a certain action level as defined by OSHA's Vinyl Chloride Standard (29 CFR 1910.1017), OSHA mandates a medical surveillance program of semi-annual measurement of liver chemistries including ALT and AST. As shown in Cave et al. however some workers who were exposed to very high levels of vinyl chloride developed liver cancer, despite having normal ALT and AST values, suggesting current vinyl chloride regulations for testing (29 CFR 1910.1017) may not be sufficient.

K18 and Hepatotoxicity – In the research study described above, the mechanism of liver toxicity was caused primarily by necrosis. Both caspase-cleaved K18 (M30) and total K18 (M65) were measured using the ELISAs and apoptosis (M30) did not appear to be a mechanism of the cell death due to harmful amounts of this chemical. However, normal liver transaminases are now recognized to occur in liver damage, regardless of the initial chemical or drug insult, and apoptosis is known to be a hallmark of certain liver damage due to disease (ie, NASH). Normal ALT has been shown in research of liver damage (alcohol [AH], fat [NASH], viral [HCV]). Depending on the insult, the mechanism of cell death may be due more to apoptosis (M30) or necrosis or both (M65) and levels have been shown to be elevated in liver disease research.

Table 2 Keratin 18 Product Overview

Product	Cell cultures	Spheroids	Xenografts	Blood samples	Apoptosis	Total cell death	Ratio Cell death mode
M30 Apoptosense® ELISA	✓	✓	✓	✓	✓	–	✓*
M30 CytoDeath™ ELISA	✓	✓	–	–	✓	–	–
M65® ELISA	✓	✓	✓	✓	–	✓	✓*
M65 EpiDeath® ELISA	✓	✓	✓	✓	–	✓	–

* These products must be used together to determine the ratio between apoptosis and necrosis.

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