CLCW Carcinogens-What You Need to Know

CLCW SME training August, 2017

Circumstances for which a SME MO can be Requested

- Veteran has a diagnosis of a presumptive condition AND >/= 30 days exposure, filed claim prior to March 13, 2017 effective date.
- Veteran has a Health Care Law (CLA) condition with at least one day of service (30 days for health care).
- Veteran has a “presumptive condition” but < 30 days exposure.
- All cancers.
- Nexus statement for any condition.

Chemical Carcinogens: What CLCW Associated Cancers and Conditions Matter *A Priori?*

- Esophageal cancer (N,H) - PCE
- Lung cancer(N,H) - PCE
- Breast cancer (N,H) - PCE
- Bladder cancer (N, H&P) – PCE
- Kidney cancer (N,H&P) – PCE, TCE
- Miscarriage (N,H) – PCE (during pregnancy)
- Adult leukemia (N,H&P) – Solvent Mixtures
- Multiple myeloma (N,H&P) - Solvent Mixtures
- Myelodysplastic syndromes and Aplastic Anemia (N,H&P)- Solvent Mixtures
- Renal Toxicity (N,H) - Solvent Mixtures
- Hepatic Steatosis (N,H) - Solvent Mixtures
- Female infertility (N,H) - Solvent Mixtures (during exposure)
- Scleroderma (N,H) - Solvent Mixtures
- Neurobehavioral effects (N,H) - Solvent Mixtures
- NHL(H*15&P)
- Liver cancers (P)
- Parkinson's disease (P)

- *N=NAS; H=CLA; P=Presumptive*

Who is the International Agency for Research on Cancer?

- 1965: IARC established in 1965 as the specialized cancer agency of the WHO, soon receives frequent requests for advice on the carcinogenic risk of chemicals.
- 1970: IARC Advisory Committee on Environmental Carcinogenesis recommends “a compendium on carcinogenic chemicals be prepared by experts.”
- 1971: Criteria established to evaluate carcinogenic risks to humans in a series of monographs.
- 1988: Series becomes IARC Monographs on the Evaluation of Carcinogenic Risks to Humans -Current Monograph is # 119
- The objective of the IARC is to promote international collaboration in cancer research.

IARC Carcinogen Classification through Volume 119

Group 1	*Carcinogenic to humans*	120 agents
Group 2A	*Probably carcinogenic to humans*	81
Group 2B	*Possibly carcinogenic to humans*	299
Group 3	*Not classifiable as to its carcinogenicity to humans*	502
Group 4	*Probably not carcinogenic to humans*	1

		Cancer in Experimental Animals		
		Sufficient	Limited	Inadequate
Cancer in Humans	Sufficient	Group 1	Group 1	Group 1
	Limited	Group 2A	Group 2B Exceptionally Group 2A	Group 2B Exceptionally Group 2A
	Inadequate	Group 2B Exceptionally Group 2A	Group 3	Group 3

CLCW Contaminants

- TCE, PCE, VC and Benzene are extensively studied compounds [IARC, ATSDR, EPA, NIOSH, CDC]
- Strongest evidence of human health effects from occupational studies of workers exposed to *higher doses and/or long term* relative to CLCW.
- TCE classified as a “known human carcinogen” IARC I (as is tobacco and wood dust)
- VC classified as a “known human carcinogen” IARC I
- Benzene classified as a “known human carcinogen” IARC I
- PCE classified as “likely to be carcinogenic to humans” IARC IIA (so is red meat consumption)

IARC Classification of Cancer Risk

Solvents	IARC classification Group 1 = Sufficient Group 2A = Limited
Trichloroethylene (TCE)	***IARC Group 1*****:** Kidney ***IARC Group 2A:*** Liver/biliary tract cancers, Leukemias/lymphomas
Perchloroethylene (PERC)	***IARC Group 2A***: Bladder
Benzene	***IARC Group 1***: Leukemia (AML)
Vinyl Chloride	***IARC Group 1***: Angiosarcoma of the liver

IARC

- The IARC process is inherently “conservative.”
- IARC classifications are a major metric and should not be ignored.
- Do not discount IARC Group 2, especially Group 2A.
- IARC is not the sole arbiter of carcinogenicity.

ATSDR January 13, 2017

*Assessment of the Evidence for the Drinking Water Contaminants at Camp Lejeune and Specific Cancers and Other Diseases

Disease	Chemicals	Meta-analysis Citations	ATSDR Conclusions
Kidney Cancer	TCE	Kelsh 2010; Scott (EPA) 2011; Karami (NCI) 2012	Sufficient evidence for causation
	PCE		Below equipoise evidence for causation
Non-Hodgkin Lymphoma	TCE	Kelsh 2010; Scott (EPA) 2011; Karami (NCI) 2013	Sufficient evidence for causation.
	PCE		Equipoise and above evidence for causation
	Benzene	Steinmaus 2008; Kane 2010; Vlaanderen 2011	Sufficient evidence for causation
Multiple Myeloma	TCE	Alexander 2006; Karami (NCI) 2013	Equipoise and above evidence for causation
	PCE		Below equipoise evidence for causation
	Benzene	Infante 2006; Vlaanderen 2011	Equipoise and above evidence for causation
Leukemias	TCE	Alexander 2006; Karami (NCI) 2013	Equipoise and above evidence for causation for all types of leukemia
	PCE		Below equipoise evidence for causation
	Benzene	Khalade 2010; Vlaanderen 2011; Vlaanderen 2012	Sufficient evidence for causation for all types of leukemia
	Vinyl chloride	Boffetta 2003	Below equipoise evidence for causation
Liver Cancer	TCE	Alexander 2007; Scott (EPA) 2011	Equipoise and above evidence for causation
	PCE		Below equipoise evidence for causation
	Vinyl chloride	Boffetta 2003	Sufficient evidence for causation
	Benzene		Below equipoise evidence for causation
Bladder Cancer	TCE		Below equipoise evidence for causation
	PCE	Vlaanderen (IARC) 2014	Sufficient evidence for causation
	Vinyl chloride		Below equipoise evidence for causation
	Benzene		Below equipoise evidence for causation
Parkinson Disease	TCE		Equipoise and above evidence for causation
	PCE		Below equipoise evidence for causation

CLCW Issues

- The majority of CLCW environmental exposures do not reach the dosage and /or duration levels seen in many of the reported and studied occupational settings which severely limits the application of this data to CLCW exposures.
- Higher dosages may exert different biologic effects than lower dosages.
- “Workers are exposed to much higher levels of TCE, PCE, benzene, and VC than are people who drink (CL) contaminated water. Therefore, the health problems seen in people who worked with TCE, PCE, benzene, and VC may not be seen in people who drank contaminated water” [ATSDR Reported health effects linked with TCE, PCE, benzene, and VC exposure in people, updated January 16, 2014].

CLCW Issues

- The current ATSDR Camp Lejeune Drinking Water Public Health Assessment (PHA- January 20, 2017) reports lowered estimates of the anticipated carcinogenic effects for Marines-in –training related to CLCW exposure of 3 years duration or less
- Primary concern from TCE and vinyl chloride exposure 1970s-to mid 1980s.
- This is in contrast to several commonly cited articles published in recent years.

CLCW Issues

- Further complicating the Camp Lejeune contaminated water evaluation is that quantifying actual exposures is difficult at best as a result of various physical effects.
- These include consideration of chemical dilution beyond the source of contamination.
- Variables from differing methods of contact, such as ingestion verses physical contact (absorption) and/or inhalation.
- Various forms of contact can be associated with differing absorption and inhalation from activities like bathing and hygiene, swimming, working (mess hall) or laundry, drinking, etc.

IARC Bladder Cancer Vol 119

Carcinogenic agents with *sufficient evidence* in humans

- Urinary bladder Aluminum production
- 4-Aminobiphenyl
- Arsenic and inorganic arsenic compounds
- Auramine production
- Benzidine*
- Chlornaphazine
- Cyclophosphamide
- **Magenta production**
- 2-Naphthylamine
- Painting
- Rubber production industry
- Schistosoma haematobium
- Tobacco smoking
- *ortho*-Toluidine
- X-radiation, gamma-radiation

Agents with *limited evidence* in humans

- 4-Chloro-*ortho*-toluidine
- Coal-tar pitch
- Dry cleaning
- Engine exhaust, diesel
- Hairdressers and barbers, occupational exposure
- 2-mercaptobenzothiazole
- Pioglitazone
- Printing processes
- Soot
- Textile manufacturing
- Tetrachloroethylene (PCE/PERC)

"Castellani's paint or magenta paint has been used to treat fungal skin infections since the 1920s. Magenta has also been used in hair dyes, cosmetic products and artist paints. Several studies have shown that people who work in dye-making factories that produce magenta have a higher risk of bladder cancer than the general population. The International Agency for Research into Cancer (IARC) classifies different things according to their cancer risk – they have listed the production of magenta as high risk, meaning there is conclusive evidence that working in such as job could cause cancer, likely because of exposure in the production process to a chemical called ortho-toluidine. However, evaluations by IARC have found no evidence of magenta ***as a product*** *increasing cancer risk. There is also no clear evidence that other ingredients in Castellani's paint, aside from the dyes that make up magenta, pose any risk of cancer."*

* Cancer Council Australia; www.cancer.org.au

What We Must Continuously Ask Ourselves

- Does the exposure result in an increased risk of disease (a risk factor is an environmental, behavioral or biologic factor confirmed by temporal sequence that if present directly increases the probability a disease will occur and if absent or removed reduces that probability) ?
- Is the exposure causal (does one factor alter the probability of another)?
- Is the exposure merely an observed association (Sir Austin Bradford Hill criteria for causation)?
- Is the exposure an inferred cause (speculative)?

"Etiology" deals with the direct causes of the disease as well as significant risk factors. Legislatures and judicial systems have the power to substitute convenience for science (i.e. creation of Presumptives).