

Date: 9/1/09
To: John Froines, Professor of Toxicology, UCLA
From: Kathleen Collins, Professor of Molecular and Cell Biology,
UC Berkeley, kcollins@berkeley.edu
Re: Summary of 8/21/09 testimony at legislative hearing

The general biological responses to DNA damage by methylation are:

1. DNA repair (if damage is at a low level),
2. Cell suicide (highly damaged human cells kill themselves or attract killers)
3. Genome mutation (cumulative increments of cancer risk)

DNA methylation reactions often yield modified bases that are unable to serve as template for a DNA polymerase. These DNA lesions will recruit repair activities both directly (by recognition of distorted DNA) and as the consequence of stalled DNA replication (when the DNA is being copied prior to cell division). However, there is growing awareness that some DNA modifications will be copied over by a DNA polymerase if they are not repaired in advance of DNA replication, thus increasing the probability of genome mutation. Genome mutation in somatic tissues (most of our body) accelerates the progression of cancer. Genome mutation in germline cells (cells that develop into sperm and egg) leads to infertility and disease inheritance.

Mechanisms of carcinogenicity of methyl halides.

Bolt HM, Gansewendt B. Crit Rev Toxicol. 1993;23(3):237-53.

“... methyl iodide, upon oral and inhalation administration to rats and mice, caused systemic DNA methylation. Specifically, 3-methyl-adenine, 7-methyl-guanine, and O6-methyl-guanine were formed¹”

O6-methyl-guanine is a particularly dangerous form of DNA methylation: it can be repaired, but it can also be replicated without repair (see below). Thus, the type of DNA methylation damage caused by methyl iodide has both short-term toxicity (from repair-induced delay of cell growth or damage-induced cell death) and cumulative long-term deleterious impact (by permanent genome mutation, leading for example to cancer).

The structural basis for the mutagenicity of O(6)-methyl-guanine lesions.

Warren JJ, Forsberg LJ, Beese LS. Proc Natl Acad Sci USA. 2006;103(52):19701-6.

“Methylating agents are widespread environmental carcinogens that generate a broad spectrum of DNA damage. Methylation at the guanine O(6) position confers the greatest mutagenic and carcinogenic potential. DNA polymerases insert cytosine and thymine with similar efficiency opposite O(6)-methyl-guanine (O6MeG). ... Our structures reveal that both thymine and cytosine O6MeG base pairs evade proofreading by mimicking the essential molecular features of canonical substrates.”

Hazardous waste classification

UC Berkeley Environmental Health & Safety (EH&S) regulations classify methyl iodide as the most toxic category of compound (zero-release, class C). This is a greater hazard level than most radioactivity (class B). See drain disposal pdf for complete guidelines.

Class designation for hazardous waste disposal

Class A includes chemicals that pose little or no hazard in dilute aqueous solution.

Class B includes chemicals of moderate hazard in dilute aqueous solution. These aqueous solutions are suitable for disposal down the drain with excess water.

Class C includes chemicals that may not be drain disposed in any amount...requests for exceptions are made to EH&S who obtains any necessary additional information and coordinates review.