

EVIDENCE THAT A "SAFE" DOSE OF MUTAGEN DOES NOT EXIST

Background: Industrialists and their paid think tanks (i.e. The Cato Institute) argue that low levels of environmental mutagens are not a cancer threat because cells possess DNA repair enzymes. Indeed, few would reach reproductive age without DNA repair enzymes. However, in order for the industrialists to be correct, DNA repair enzymes must be 100% efficient in every cell preceding every round of DNA replication 100% of the time! Listed below is unequivocal evidence that DNA repair mechanisms are by no means failsafe.

1. The physical principle of molecular mass action dictates that even the best DNA repair system in the most healthy person can not detect and repair all premutational lesions prior to DNA replication. Assuming it were true, many people are "repair compromised" because of their genotype or due to their state of health. Are you homozygous normal for all DNA repair enzymes - are you healthy?
2. It has been unequivocally established that humans accumulate somatic mutations as they pass through life. This unambiguously demonstrates that repair pathways are not failsafe.
3. **We now know that more than 98% of all human cancers are caused by environment-induced somatic mutations.** If DNA repair mechanisms were failsafe, this remarkable fact could not be true. We also know that the incidence of numerous cancers continue to increase (4.3% per year since 1992 for liver). This further confirms that repair pathways are by no means failsafe. (see point 9 below)
4. Most of the inherited gene defects that predispose an individual to cancer (i.e. the 1-2 % of cancers that are not due to environment-induced somatic mutations) are mutations in genes that encode DNA repair enzymes.
5. Current animal assays vastly underestimate the "life time" risk of carcinogens in humans.
 - a. The mouse genome can only accumulate mutations for two years. What appears to be a threshold level in mice is not likely to define a threshold level in humans.
 - b. In animal assays, increasing doses of carcinogen activate many DNA repair pathways providing a cellular defense against carcinogenic mutations. Thus, abnormally high doses must be given to establish the TD-50 (the dose that induces tumors in 50% of the animals). It is this abnormally high dose that is often used in attempts to establish human risk.
 - c. In the context of the above point, it is now known that at very low doses of mutagen, the biochemical defense pathways are not upregulated. Taken together, these facts argue that a life time exposure to very low doses of carcinogen may be worse than short term exposures to higher doses.
 - d. Assays for chemical carcinogens in experimental animals are also flawed because researchers can not and do not examine all tissues following death and because "initial primary lesions" (a few transformed cells) can not be detected. Additionally, typical experiments only use about 300 animals. This number is too low to detect only but the most potent of carcinogens.
6. Currently we are exposed not to one specific mutagen but to thousands. No animal assay comes close to evaluating the combined risk of these substances. Additionally, no current assay takes into

account the amount of carcinogenic pharmaceuticals (i.e. Tylenol, Imuran, Methotrexate, Lotramin, steroids, etc. etc.) or alcohol a person may consume. Alcohol and most drugs upregulate bioactivation pathways and/or inhibit DNA repair pathways. Finally, no assay can take into account the extent to which detoxification enzymes and DNA repair enzymes are inactivated by mercury, lead, arsenic and other heavy metals, carbon monoxide, and other environmental pollutants like PCBs.

7. Today, 46 percent (essentially half) of all white males will be diagnosed with cancer in their life time. Additionally, the tissues most in harms way from environmental chemicals (liver, thyroid, prostate, kidney, skin, testis, uterus, breast) show the highest rate of cancer increases since 1992. Liver cancer increased at a rate of 4.7% per year since 1992.

8. **DNA is a chemical molecule. The only way to modify a chemical like DNA is with another chemical through a chemical or physical-chemical reaction (alkylation, intercalation, strand breakage).** Viruses like hepatitis B and C destroy large portions of the liver placing an increased chemical work load on the liver and place the liver in greater likelihood of a cancer-causing mutation. These viruses do not directly activate oncogenes in liver cells. Additionally, these viruses and bacteria like *H. pylori* cause tissue inflammation and increased cell division which also places these tissues at increased risk of mutation.

9. **The only people that argue current levels of mutagen are at "safe levels" are those who own or work for concerns that profit by the use of mutagenic chemicals.** To an educated populace this alone should be enough to discount the argument.