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LETTER TO THE EDITOR

Further Considerations for the Implausibility of Leukemia Induction by Formaldehyde

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We fully agree with Thompson and Grafstrőm for the "need to further examine the epidemiological evidence for the association between formaldehyde exposure and leukemia." We do not have any data that support or refute their proposal that alcohol dehydrogenase-3 and nitrosothiol signaling represent a possible alternate mechanism that could be involved in leukemogenesis.

We do have additional data supporting the lack of plausibility that inhaled formaldehyde is causally associated with the induction of leukemia. New inhalation studies have been conducted on nonhuman primates with exposures of 2 or 6 ppm [$^{13}CD_2$]-formaldehyde for 6 h/day for 2 days. In this study, a greatly improved nano ultra performance liquid chromatography-mass spectrometry/mass spectrometry (UPLC-MS/MS) method with a limit of detection of 20 amol on column was used to measure both endogenous and [$^{13}CD_2$]-OH-methyl dG adducts in nasal epithelium and bone marrow. Endogenous and [$^{13}CD_2$]-OH-methyl dG adducts were readily measured in 20–30 μg of nasal DNA from nonhuman primates; however, no [$^{13}CD_2$]-OH-methyl dG adducts were detectable in up to 312 μg of bone marrow DNA. In contrast, high numbers of endogenous OH-methyl dG adducts were present in bone marrow DNA. The number of endogenous adducts in the 312 μg of bone marrow DNA was 20.8 adducts per 10^7 dG. If one makes a worst-case scenario and assumes that exogenous adducts were just below the limit of detection in this sample, less than 8.3 [$^{13}CD_2$]-OH-methyl dG adducts per 10^{11} dG could have existed. This would mean that less than one exogenous DNA adduct was present for every 12,500 endogenous formaldehyde adducts. It is highly implausible that 1/12,500 identical DNA adducts could drive the biology that leads to carcinogenesis.

Furthermore, we have conducted molecular dosimetry studies on rats exposed by inhalation to 0.7, 2.0, 5.8, 9.1, or 15.2 ppm [$^{13}CD_2$]-formaldehyde for a single 6-h exposure. The exogenous [$^{13}CD_2$]-adducts were formed in a highly nonlinear fashion, as demonstrated by the fact that a 21.7-fold increase in exposure (0.7–15.2 ppm) formed 286-fold higher amounts of exogenous DNA adducts in rat nasal epithelium. The ratio of exogenous to endogenous OH-methyl dG was 0.011 ± 0.001, 0.033 ± 0.006, 0.19 ± 0.04, 0.60 ± 0.17, and 2.79 ± 1.08 for 0.7, 2.0, 5.8, 9.1, and 15.2 ppm formaldehyde exposure, respectively. Bone marrow from the rats exposed to 15.2 ppm [$^{13}CD_2$]-formaldehyde was also analyzed with our more sensitive nanoUPLC-MS/MS method, and exogenous formaldehyde adducts were below the detection limit of 20 amol. In contrast, endogenous OH-methyl dG adducts were ~15 adducts per 10^7 dG. Thus, less than one [$^{13}CD_2$]-adduct could be present in 1500 identical endogenous adducts in a rat exposed to 15.2 ppm [$^{13}CD_2$]-formaldehyde for 6 h. Again, it is highly implausible that this one adduct could induce malignant transformation in the bone marrow when 1500 endogenous adducts do not.