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August 28, 2002

Gary Gill
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State of Hawaii Department of Health
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Dear Mr. Gill:

Thank you for your response to my letter of August 15, 2002 regarding the experimental use of caffeine to kill frogs here in Hawaii. Your letter has ignored many of the issues we have raised, such as the use of human subjects as part of this assessment of the effect of caffeine spraying, which requires informed consent and an Institutional Review Board to oversee the experiment. You also ignored the many physiological risks caffeine poses to the public, including those groups known to be at high risk such as pregnant women, toddlers, and anyone with circulatory disease or high blood pressure.

You chose to limit your response to our comment about the mutagenic nature of caffeine, which you question since it is not listed as a carcinogen by the National Toxicology Program or the California EPA's Reproductive and Cancer Hazard Assessment Program. You have asked for me to support my contention that caffeine is a mutagen.

According to the application made to the EPA by the Hawaii DOA and DLNR for Section 18 exemption of caffeine, it states on page 8 that, "One publication has also indicated that caffeine induces chromosomal breakage in fruit fly, higher plants, and a variety of microorganisms." The EPA's Section 18 label for this experimental use of caffeine states that, "Some studies have indicated possible chromosomal damage at high levels of application, therefore applications should not be made to high-valued plants."

From a different source is a statement made by the Sandoz Pharmaceuticals company about its product Cafergot, which contains caffeine. In the 1996 Physicians' Desk Reference it states, "Caffeine is known to cross the placenta and has been shown to be teratogenic in animals."

It is interesting to note that in 1980, the FDA issued a warning advising pregnant women to limit their exposure to caffeine, since at high doses, caffeine seemed to have a teratogenic effect in mammals.

The MSDS-CCOHS (Material Safety Data Sheets from the Canadian Center for Occupation Health and Safety), dated January 9, 1997, states, "The Chronic Effects: There is limited evidence that when overexposure occurs, Caffeine is teratogenic and tumorigenic in laboratory animals. There is also limited evidence that Caffeine is mutagenic in laboratory cell cultures. Until further testing has been done, it should be treated as a possible teratogen, tumorigen, and mutagen in humans."

Again, according to the National Institute of Environmental Health Sciences, "At extremely high doses (much higher than the average person can consume on a regular basis), caffeine can be a mutagen (capable of making changes at the cellular level), a potential teratogen (capable of affecting the fetus) and a probable carcinogen as well." (http://www.niehs.nih.gov/external/faq/clean.htm).

A recent review article on the teratogenicity of caffeine is also instructive. "It should be noted that evaluation of the developmental risks of caffeine based solely on epidemiological studies is difficult because the findings are inconsistent. Even more important, is the fact that caffeine users are subject to multiple confounding factors that make analyses difficult and prevent investigators from reaching definitive conclusions. For example, the caffeine content of foods and beverages can vary considerably, which can interfere with obtaining valid interpretations from many human studies." It goes on to state, "the overall conclusion is that caffeine is a chemical, among a long list of drugs and chemicals, that may have the potential to injure the embryo if used in marked excess." (MS Christian, RL Brent. Teratogen Update: Evaluation of the reproductive and developmental risks of caffeine. Teratology, Vol 64 Issue 1 (2001) p.51-78.)

Perhaps most sobering of all is the statement that, "Overindulgence in xanthine beverages may lead to a condition that might be considered one of long-term poisoning. *There are also rare persons who are so sensitive to caffeine that even a single cup of coffee will cause a response bordering on the toxic.*" (Goodman and Gilmans's The Pharmacological Basis of Therapeutics. 8th ed. NY, NY Pergamon Press, 1990.

You cannot ignore the studies that show mutagenicity to humans, even if some studies disagree. There is not enough information at present. However, clearly, caffeine has not been proven safe. The key question is whether the residents of Hawaii are going to add to the bulk of caffeine research by being forced to participate in the proposed caffeine experiment.

Your letter also mentions that caffeine is quickly metabolized and eliminated from the body, implying that mutagenicity is unlikely since the body does not accumulate caffeine. However, several studies on animals have shown that a *single* high dose of caffeine was enough to produce embryonic death and malformations. (References available, if requested.) This means that accumulation of caffeine is not necessary to elicit a mutagenic response. Further, the daily consumption of caffeine by the average citizen today provides a constant exposure to caffeine.

Keep in mind, too, the synergistic and antagonistic effects of caffeine in combination with other drugs. For example, the combined action of caffeine and histamine is greater than the sum of their individual actions with respect to the secretion of pepsin and stomach acid. (By the way, caffeine is known to cause ulcers.) Caffeine also may enhance the cardiac inotropic effects of beta-adrenergic stimulating agents. Caffeine has also been reported to increase the metabolism of several drugs, including aspirin and phenobarbital. And caffeine has been shown to increase the teratogenic effect of other drugs, such as acetazolamide, mitomycin C, hydroxyurea, and 5-fluorouracil.

There is also a relationship between one's level of health and caffeine's effects. Liver damage, for example, impairs caffeine metabolism and clearance, as would kidney disease. These confounding issues have been ignored in this letter, but are nevertheless important to keep in mind when considering the potential effects of the caffeine experiment on the Hawaiian public.

Interestingly, since caffeine is so widely used, and since many billions of dollars are made annually selling coffee, chocolate, tea, and caffeine-containing beverages, you can understand why caffeine's effects on health are controversial. Nicotine, alcohol and caffeine are commonly used drugs in our culture, with large industries invested in their continued consumption. All three have been claimed to create health problems, as well as to provide health benefits. Like most things, there are advantages and disadvantages to these drugs, and those invested in selling a product point out the advantages of their product. This explains why caffeine has been shown to be a mutagen in many studies, yet continues to not be labeled as such. With billions of dollars invested in caffeine, it would take unequivocal evidence, and mountains of it, to get an adverse labeling of caffeine. But this is politics, not science, or preventative medicine.

Finally, I was wondering if you realized that the State of Hawaii has a huge conflict of interest

regarding this proposed use of caffeine as a pesticide. The University of Hawaii, which is promoting this use of caffeine, also owns the patent for the caffeine gene, which was granted in 1999! The developer of this patented gene, Dr. John Stiles, was a Dean at the University, and left to start Integrated Coffee Technologies, Inc., (ICTI), which has the exclusive license for the use of this patent. ICTI has been working on an uncaffeinated coffee by blocking this gene. However, Dr. Stiles has told me that the caffeine gene could also be placed in bacteria to produce genetically engineered caffeine in the laboratory. He said the market value for caffeine is currently too low to justify its production this way, which could produce cheap GE caffeine. However, if caffeine does become approved as a pesticide, the market value of caffeine would increase. This means that the University's patent and its license of that patent to ICTI would increase tremendously in value if caffeine becomes approved as a pesticide.

The State of Hawaii has a clear conflict of interest in this caffeine business and its promotion as a pesticide. ICTI has stockholders, some of whom could be in the government. Frankly, I don't know who the stockholders are. But with the State and Federal governments biased towards performing a caffeine experiment here in Hawaii, it makes one wonder. Is this all about frogs, or is it really all about caffeine and money?

Remember, the frogs are not a health threat. The caffeine is.

Your position is that we have insufficient data to state with certainty whether caffeine can cause mutations and cancer in people. However, should we try the caffeine experiment and see? I hope not! And this ignores the host of other physiological and psychological effects that caffeine is known to cause. Caffeinism is already a common problem for many. Given the high doses of caffeine many people currently consume each day, acute caffeine poisoning is a real concern. And, as I have mentioned in previous letters, there is no antidote for caffeine poisoning.

If you cared about prevention, we would agree that it is prudent to take the side of safety. Since caffeine could be a mutagen in humans, then prudent avoidance of its use could prevent a catastrophe.

Surely, if the interest were there, an alternative to caffeine that is safe could be found to help control the frog numbers. The way it seems now, however, the money is on caffeine. The fact that the U of H owns a patent for the caffeine gene casts serious doubt on the integrity of this caffeine proposal, and its true purpose.

And keep in mind that we are only talking about frog control, not frog eradication. Like the mongoose, they are here to stay, according to the DOA and DLNR. Caffeine's ultimate effect on the frogs is still unknown, although it is realized that the caffeine will kill much more than frogs, and may pose a threat to the water supply, as well as to aquatic life.

Caffeine is currently found in water supplies in several countries, including the mainland U.S., as a contaminant. It is said to display "very high mobility" if released in the soil. This means it will probably pollute our water supply. I know that caffeine proponents will say they expect that it will decompose quickly in water and pose no threat at low concentrations. But again, nobody really knows for sure. That's why this is an experiment with the environment, as well as with the public.

What I see, then, is a publicly funded caffeine experiment on the people and environment of Hawaii designed to get approval for caffeine as a pesticide thereby increasing the value of caffeine and making the production of GE caffeine a profitable enterprise. It may have nothing really to do with frogs. The fact that we are being told by the USDA Wildlife Services that there is no alternative to caffeine to kill the frogs reinforces this view, particularly since the caffeine has been proposed by this same agency, and this same agency will be receiving millions of dollars per year for its administration. In addition, the USDA is doing the EA on the use of caffeine, making the conflict of interest even worse.

Do your job, Mr. Gill! Protect the people and environment of Hawaii. Let the USDA Wildlife Services, DOA, and DLNR come up with a *PROVEN SAFE* method for frog control. The public needs to be protected from risks, not placed at risk. And since caffeine could be lethal and mutagenic, the risks of its use are too great, particularly when the potential benefit of its use simply amounts to ongoing frog control.

Sincerely,

Sydney Ross Singer
Director, CHIRP

Cc: Dr. Lyle Wong — DOA
Gilbert Coloma-Agaran – DLNR
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