# Perspectives | Correspondence

## Testing Needed for Acesulfame Potassium, an Artificial Sweetener

In their article "First Experimental Demonstration of the Multipotential Carcinogenic Effects of Aspartame Administered in the Feed of Sprague-Dawley Rats," Soffritti et al. (2006) present interesting data on the carcinogenic effects of long-term exposure to aspartame, an artificial sweetener, in experimental animals (rats).

Recently, aspartame was supplanted as the leading artificial sweetener by sucralose, marketed in the United States under the trade name Splenda (McNeil Nutritionals, LLC, Ft. Washington, PA). As of 2005, Splenda was reported to have > 50% of the market for artificial sweeteners, while aspartame [Equal (Merisant Company, Chicago, IL); NutraSweet (NutraSweet Property Holdings Inc., Chicago, IL)] had < 20% (Associated Press 2005). Splenda is typically used in sweetener blends, most frequently with acesulfame potassium (CAS RN 55589-62-3) (Sunett; marketed in the United States by Nutrinova, Somerset, NJ).

The Food and Drug Administration's (FDA) multiple approvals of food additive petitions (FAPs) for acesulfame began in 1988 (FDA 1988), and culminated in 1998 with approval of the use of acesulfame in soft drinks (FDA 1998), historically the largest single use of artificial sweeteners. All of the FDA's approvals of FAPs for acesulfame were grounded on the conclusion that safety studies, including long-term animal tests of acesulfame carried out for Hoechst, the manufacturer of the chemical, in the Netherlands in the 1970s, were adequate and the test results indicated safety.

The 1970s tests of acesulfame—two tests carried out in rats and one in mice—are inadequate to establish lack of potential carcinogenicity. Here are a few reasons why the tests are inadequate [Center for Science in the Public Interest (CSPI) 1996]:

- Subchronic tests were not conducted for the rats and mice used in the tests on which the FAPs rested
- It is likely the minimum toxic dose/maximum tolerated dose (MTD) was not achieved in the rat and mouse studies
- Randomization of test groups was not carried out properly
- Mice were held on test for only 80 weeks, rather than the 104 weeks characteristic of National Toxicology Program (NTP) bioassays

- Animal husbandry and monitoring of animals on test were evidently poor, as indicated by high disease rates in the animals and extensive autolysis of tissues.

Even with the flaws in design and execution of the Hoechst tests, results indicated an association between treatment with acesulfame and carcinogenesis (CSPI 1996).

Working-level staff members at the FDA identified deficiencies in the acesulfame tests in the 1980s (McLaughlin 1986; Taylor 1986). Thus, an FDA staff member (Taylor 1986) noted in 1986, when the FDA had decided to accept the Hoechst studies, that

> The question remains whether these studies are sufficiently definitive or rigorous in light of the potential for widespread, [sic] high exposure to acesulfame K in all group [sic] in the population.

In 1996, the CSPI nominated acesulfame for testing in the NTP bioassay program (CSPI 1996), and provided the NTP with detailed information on the Hoechst tests and their flaws. Although an individual familiar with test design and implementation could have concluded with ease that the Hoechst tests were not consistent with the criteria established for NTP bioassays or the test guidelines set out in the FDA's *Redbook* (FDA 1982), and that it was likely that, at some point, many people would be exposed to acesulfame, the NTP rejected CSPI's nomination.

In 2003, the NTP announced the results of tests of both aspartame and acesulfame in genetically modified mice (GMM) (NTP 2005). Both chemicals gave negative results in the tests, carried out in two strains of GMM.

The NTP's final report on those GMM studies (NTP 2005) noted that aspartame and acesulfame had been selected as "negative controls" for validation tests for the GMM models. The chemicals did indeed test negative, but that negative result did not advance our understanding of potential carcinogenicity of acesulfame. Regarding the GMM tests of aspartame and acesulfame, Martha Sandy of the California Environmental Protection Agency, stated that

> [N]egative results [in the GMM tests] are not informative as to the test substance's carcinogenicity, and point to the need to conduct standard two-year carcinogenicity studies. At this time, transgenic models cannot replace the two-year bioassay and it would be unwise to list a chemical as safe for human exposure based upon negative results in not yet validated model systems. (Sandy 2003)

The findings of Soffritti et al. (2006) of multipotential carcinogenesis in rats fed aspartame over their lifetimes provide support for Sandy's (2003) statements.

I have sent the NTP a new nomination of acesulfame for 2-year bioassay testing (Karstadt 2006).

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## Acesulfame Potassium: Soffritti Responds

Karstadt makes an important point regarding the need for more adequate long-term carcinogenicity testing of the artificial

sweetener acesulfame K. The issues raised in her letter stimulated me to offer some additional considerations.

As reported in a previous paper (Soffritti et al. 1999), one of the most important issues in environmental and industrial carcinogenesis is how to deal with diffused carcinogenic risks, to which most of the planet's population may be exposed. These carcinogenic risks are represented by *a*) agents that are slightly carcinogenic at any dose; *b*) low or extremely low doses of a carcinogenic agent of any kind; or *c*) mixtures of small doses of carcinogenic agents.

Epidemiologic and experimental studies are fundamental in the identification and quantification of diffused carcinogenic risks, but they must be designed and conducted to be as powerful as possible with adequate methodology. In the case of experimental studies, it is not sufficient to follow the standard protocol used in ordinary experiments. Instead, it is necessary to conduct studies that may be defined as "mega-experiments," using a vast number of animals (at least 200–1,000 per experimental group) in order to express a marked difference in the variation of effects, and exposing the animals in all phases of development to allow the agent to express its full carcinogenic potential.

It is based on this rationale that the European Ramazzini Foundation performed a mega-experiment on 1,800 rats and demonstrated that, in our experimental conditions, aspartame is a multipotential carcinogenic agent (Soffritti et al. 2005; Soffritti et al. 2006).

The results of our study (Soffritti et al. 2005, 2006) attracted the attention of the scientific community, consumer and industry associations, and the national and international agencies responsible for food safety. Among various comments, the opinion expressed on 5 May 2006 by the European Food Safety Authority (EFSA 2006) and the general interpretation of an epidemiologic study conducted by the National Cancer Institute (NCI 2006) necessitate comment on our part.

In examining the raw data of our study, the EFSA (2006) observed a high incidence of chronic pulmonary inflammation in males and females in both treated groups and in the control group. Based on this observation, it was concluded that "the increased incidence of lymphomas/leukemias reported in treated rats was unrelated to aspartame, given the high background incidence of chronic inflammatory changes in the lungs." In my opinion, this conclusion is bizarre for the following reasons:

First, the EFSA (2006) overlooked the fact that the study was conducted until the natural death of the rodents. It is well known that infectious pathologies are part of the natural dying process in both rodents and humans.

Second, if the statistically significant increased incidence of lymphomas/leukemias observed was indeed caused by an infected colony, one would expect to observe an increased incidence of lymphomas/leukemias not only in females but also in males. The EFSA (2006) did not comment on this discrepancy in their logic.

Finally, in support of the hypothesis regarding the safety of aspartame, the EFSA (2006) cited the negative results of recent carcinogenicity studies carried out in transgenic mice by the National Toxicology Program (NTP); the ESFA did not mention that, because the NTP studies on genetically altered mice were performed using a new experimental model, the NTP subcommittee unanimously agreed "there is uncertainty whether the study possessed sufficient sensitivity to detect a carcinogenic effect" (NTP 2005).

Interestingly, the same scrutiny applied to our study has not been applied to a recent abstract published by Lim et al. (2006) from the NCI diet questionnaire survey (NCI 2006) in which self-reported aspartame consumption showed no increases in either leukemia/lymphomas or brain cancer. These results have been used by industry, the EFSA, and others to argue that aspartame is not a risk for humans, in spite of our animal study results. Without specific information on each individual's consumption rate and duration it is difficult to assess the power of the survey, in spite of the large number of participants. The second related issue is whether aspartame is an early- or late-stage carcinogen. If it is an early-stage initiator of cancer, then reporting the lack of effects in older individuals who have not consumed aspartame since early childhood would be expected to show little or no increased cancer (Hoel 1985).

The safety—in particular, the noncarcinogenicity—of today's most widely diffused artificial sweeteners and their blends is largely based on studies conducted decades ago. I second Karstadt's nomination of acesulfame K for further study; however, I add that it should be evaluated using a long-term mega-experiment.

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## Chemical Mixtures: Greater-than-Additive Effects?

Various combinations of chemicals are being detected in the environment with increasing frequency. This has raised awareness that we are not exposed to individual chemicals in isolation and heightens concern that the toxicity of individual chemicals may not represent toxicity when the chemicals are present in combination. Of greatest concern is that chemicals in combination may elicit synergistic toxicity that goes undetected in evaluations of individual chemical toxicity.

In a recent article, Hayes et al. (2006) assessed the effects of nine pesticides individually (at 0.10 ppb) and in combination (each at 0.10 ppb) on time to foreleg emergence and time to complete tail resorption in *Rana pipiens.* Both end points are measures of larval development in frogs. The authors reported that the pesticide mixture had a much greater effect on these developmental parameters than did the individual chemicals; they concluded that estimating ecologic risk of pesticides on amphibians using studies that examine single pesticides may lead to gross underestimates of the role of pesticides in amphibian declines. Clearly,

Hayes et al. implied that the combined effect of the nine pesticides is greater than the sum of the individual chemicals. But is this speculation of synergy warranted from these data?

To invoke synergy, one must—at a minimum—exclude the possibility of concentration or response additivity. Concentration additivity may appear as synergy when individual constituents, sharing the same mechanism of toxicity, in a mixture are all present below the threshold concentrations required for toxicity. However, in combination, the joint concentration of the constituents exceeds that threshold concentration, resulting in significant adversity. These experiments were not designed to assess concentration additivity, so no judgment can be made either in favor of or against the possibility that the toxicity of the mixture represented concentration additivity. However, individual responses to the nine pesticides were shown in graph form (Figure 1; Hayes et al. 2006), which allows for an assessment of response additivity for the mixture. Eight of nine pesticides prolonged the time to foreleg emergence, and nine of nine chemicals prolonged the time to tail resorption. However, these effects were not statistically significant, with the exception of the effects elicited by propiconzole.

We subjected these data to analyses for response additivity under the assumption that the observed effects were real but were not statistically significant due to the low power of the experimental design. A description of the response additivity model is available on our website [Computational Approach to the Toxicity Assessment of Mixtures (CATAM) 2006a] along with a mixtures toxicity calculator used in these analyses (CATAM 2006b). The response addition model predicted that the mixture of pesticides would prolong the time to foreleg emergence from 44 days to 60 days and the time to tail resorption from 56 days to 67 days. Hayes et al. (2006) determined that the pesticide mixture extended these developmental time points to 59 ± 2 days and 70 ± 2 days, respectively (mean ± SE; these values are our best estimates from Hayes et al.'s Figure 2). Thus, response addition alone explains the toxicity associated with a pesticide mixture. There is no need to invoke greater-than-additive effects and no need to raise concern that mixtures of these pesticides cause unexpected toxicity.

Toxicity of mixtures is a perplexing problem that warrants significant investigation. However, when assessing the toxicity of chemical mixtures, it is prudent to test the null hypothesis of no interactions. Only upon rejection of this hypothesis should the possibility of synergistic interactions be considered. In response to the question posed by Hayes et al. (2006) in the title of their article—"Pesticide Mixtures … Are We Underestimating the Impact?"—the evidence presented suggests that the answer is "no."

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## Chemical Mixtures: Hayes Responds

LeBlanc and Wang point out that we did not demonstrate synergy; they stated that "to invoke synergy, one must—at a minimum—exclude the possibility of concentration or response additivity." In fact, we did not "invoke synergy": in our article, not once did we use the word "synergy." LeBlanc and Wang themselves "invoke synergy" simply to show that it cannot be invoked from the current study; their problem is with what they inferred from our article, not with any claims that we made.

LeBlanc and Wang also point out that our "experiments were not designed to assess concentration additivity, so no judgment can be made either in favor of or against the possibility that the toxicity of the mixture represented concentration additivity." We agree. This was not the aim of the study. In fact, LeBlanc and Wang's thesis here is merely a restatement of our own conclusions:

The present effects of mixtures cannot be assigned to the categories of concentration additive or response additive. (Hayes et al. 2006; p. 47)

and

The examinations needed to characterize pesticide interactions as concentration additive or response additive … are difficult to design and carry out and present new challenges to regulators. Such studies are necessary, however (Hayes et al. 2006; p. 48)

Finally, LeBlanc and Wang examined our data for response additivity using a simple model and testing select parameters that fit their model while ignoring others. In our study we examined effects of nine pesticides alone (0.1 ppb) or in three different mixtures at 0.1 ppb and 10 ppb on leopard frog (*Rana pipiens*) larvae. Each treatment (30 larvae/tank) was replicated three times (1,350 larvae total). We assessed effects on 10 parameters: time to foreleg emergence (FLE) and time to complete tail resorption (TR), snout-vent length (SVL) and body weight (BW) at metamorphosis, mortality, gonadal development, thymus histology, disease rates, and the interaction between time to TR and SVL and BW at metamorphosis. Yet, according to LeBlanc and Wang, we simply

assessed the effects of nine pesticides individually (at 0.10 ppb) and in combination (each at 0.10 ppb) on time to foreleg emergence and time to complete tail resorption.

LeBlanc and Wang used their simple model to show that the effects of one of the pesticide mixtures on developmental time are predictable from the nonsignificant effects of the individual pesticides. Although they predicted the effects of a single pesticide mixture on a single variable, can their model predict the effects of even the single pesticides (propiconazole, λ-cyhalothrin, and atrazine) on the interaction between development and growth (Figure 5; Hayes et al. 2006), when none of these compounds significantly affected development alone and only atrazine affected size alone? Can their model predict the effects of atrazine plus *S*-metolachlor on the relationship between development and size or explain why the "inert" ingredients in the commercial mixture (Bicep II magnum; Syngenta Crop Protection U.S., Research Triangle Park, NC) appear to reduce this effect? Most certainly, the 70% meningitis infection rate in the surviving animals exposed to the nine-compound mixture cannot be predicted from exposure to the single pesticides, where disease rates were zero. The effect on development was the only parameter that fit LeBlanc and Wang's model and thus explains their reason for focusing on this single measure and ignoring the other nine parameters we measured.

In conclusion, the questions raised in our article (Hayes et al. 2006) can be answered only with empirical evidence obtained from appropriately designed and carefully conducted laboratory experiments, not by simplified models that ignore interactions between independent variables and relationships between dependent variables. Finally, and most important, our data

clearly show that examining individual pesticides one at a time does not reveal the magnitude of effects of low-dose chronic exposure to pesticide mixtures and thus does not allow us to accurately assess their impacts on amphibians. Practically all of the chemicals we examined had no significant effects alone, but this was certainly not the case when they were combined. Whether or not these interactions are response additive, concentration additive, or synergistic is irrelevant to the real question: Are we underestimating the impact? If we continue to base assessments on examinations of single compounds, the answer is "yes."

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## Comparing Risk of West Nile Virus against Risk of Adulticiding

Peterson et al. (2006) compared the risk of ground-based ultra-low-volume (ULV) adulticiding against the risk of West Nile virus (WNV). They concluded that

[B]y virtually any current human-health measure, the risks from infection by WNV exceed the risks from exposure to mosquito insecticides. Therefore, perceptions that human-health risks from the insecticides used to control adult mosquitoes are greater than the risks from WNV currently cannot be supported by the current scientific evidence.

We appreciate their elegant analysis of health risks associated with residential exposure to ground-based ULV adulticides, and we concur that such risks are very low. However, we are concerned that their risk–risk comparison may be misinterpreted to indicate that the human health risk associated with adulticiding is more than offset by its potential for WNV disease reduction. Peterson et al. (2006) did not provide data to support this. Such a risk–benefit comparison requires at least two refinements.

First, it needs to take into account intervention effectiveness. Although it is not unreasonable to expect some benefit, it is unlikely that adulticiding is completely (or even mostly) effective. Hence, a risk–benefit comparison would need to address the likely situation of adulticiding being substantially < 100% effective, for example, by reducing estimates of adulticiding-based benefit by a factor of $1/x$, where $x$ represents the effectiveness of adulticiding.

Second, it needs to discount benefit based on upstream interventions. Adulticiding often takes place in the context of an integrated mosquito/WNV management program. In this situation, upstream approaches (e.g., larviciding, personal protection) discount the attributable benefit of downstream interventions (e.g., adulticiding). For example, use of larviciding and personal protection, respectively, providing $y$ and $z$ effectiveness, reduces the potential benefit of adulticiding by a factor of $1/[(1 - y) \times (1 - z)]$.

Where upstream interventions are used and are fairly effective and adulticiding is not (or even if it is), adulticiding-attributable disease reduction may by substantially less than overall WNV risk. For example, if larviciding is 75% effective, personal protection 90% effective, and adulticiding 10% effective, the risk reduction achieved through adulticiding would be 1/400th of the overall risk of WNV-related disease; that is,

Overall risk/$\{1/[(x) \times (1 - y) \times (1 - z)]\}$.

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## West Nile Virus: Peterson et al. Respond

We thank Schofield et al. for their interest in our article and for their comments. We would like to clarify that Peterson et al. (2006) is simply a screening-level (tier 1) risk assessment in which we separately and conservatively examined the residential human risks from exposure to West Nile virus (WNV) and mosquito adulticides. As with all screening-level risk assessments, our assessments were not refined, but they did reveal the magnitude of risk compared to relevant end points. As Schofield et al. point out, our article should not be misinterpreted to indicate that the health risks associated with adulticiding are offset by its potential for WNV reduction. This is because we did not conduct a risk–benefit assessment, which was beyond the scope of our study.

Our article (Peterson et al. 2006) represents an initial step in an ongoing multiyear analysis of risk issues associated with certain vectorborne diseases and vector management strategies. We plan to address some of the issues Schofield et al. raise in subsequent papers.

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