

November 8, 2004

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2 pages via fax (513-627-1587) and U.S. postal mail

Dear Barbara:

We have just uncovered more important information relevant to the Iams-funded mouse study at Purdue University, which we talked about at length in our letter dated November 1, 2004. Since we agreed to your request for more time in formulating your response, we kindly request a similar courtesy—in your detailed response, please also address all of the points made in this letter dated November 8, 2004.

As we mentioned in our November 1 letter, Ms. Kelly Vanasse of Iams said the following in defense of the Purdue mouse study: *“The study is also seeking markers of bone and muscle atrophy that could be applied to investigating bone and muscle loss/healing in dogs.”*

Such markers already exist. In our November 1 letter, we cited the work of Dr. Daniel C. Richardson who had found serum and urinary markers relevant to the investigation of bone loss and healing in dogs. In this letter, we will detail three studies that have identified molecular and cellular markers relevant to the investigation of muscle loss and healing. The current knowledge of these markers negates any justifiable need to subject more animals to painful muscle-atrophy experiments to find what has already been studied and documented *ad infinitum*.

1. Cros, N. *et al.* “Upregulation of M-creatine kinase and glyceraldehyde-3-phosphate dehydrogenase: two markers of muscle disuse.” *Am J Physiol.* 1999 Feb; 276 (2 Pt 2): R308-16.

Using a hindlimb suspension model in rats, Cros discovered that “muscle creatine kinase mRNA and protein and glyceraldehydes-3-phosphate dehydrogenase mRNA [were] upregulated in unweighted muscles.” Cros also notes, “Muscle creatine kinase upregulation was shown to be an excellent, and the earliest, marker of muscle disuse at mRNA and protein levels.” Clearly such excellent markers would be more than sufficient to suit Iams’ needs.

2. Baldwin, K.M. *et al.* “Atrophy responses to muscle inactivity. I. Cellular markers of protein deficits.” *J Appl Physiol.* 2003, 95: 781-790.

In this study, Baldwin characterizes “the cellular processes linked to marked muscle atrophy [induced in rats].” He notes that “two key [cellular] factors contributing to the muscle atrophy ... are 1) a reduction in ribosomal RNA that is consistent with a reduction in protein translational capacity, and 2) insufficient mRNA substrate for



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translating key sarcomeric proteins comprising the myofibril fraction, such as MHC [myosin heavy chain] and actin.” Again, these markers could easily be used by Iams to suit its needs.

3. Baldwin, K.M. *et al.* “Atrophy responses to muscle inactivity. II. Molecular markers of protein deficits.” *J Appl Physiol.* 2003, 95: 791-802.

In this study, Baldwin “examined the expression of several molecular markers of protein balance in response to skeletal muscle atrophy [induced in rats].” Baldwin notes that skeletal muscle atrophy and protein deficits due to inactivity occur by “the coordinated events governing processes that impact 1) the reduced transcriptional activity and translational capacity (mRNA substrate and ribosomal RNA) involving key proteins comprising the sarcomeric fraction of the muscle (and other key fractions as well); and 2) the apparent upregulation of genes impacting the degradation processes governing muscle protein breakdown. ... These collective alterations bring about a rapid and marked wasting of the inactive muscle.”

The most telling point about all of these markers of muscle atrophy found in rats is that they are all translatable to mice, *and even to dogs—which is what Iams wants.* According to Baldwin: “[A]ny molecular marker for atrophy that can be identified in most rat models used in the study of muscle atrophy most likely will apply to mice and probably dogs, especially if the specific atrophy is applied to these animals. I think this is the case because of the universality (*sic*) of [the] atrophy process across (*sic*) different species including humans.”

Based on Cros and Baldwin’s findings, Iams’ justification for subjecting live mice to induced muscle atrophy, in an effort to find relevant markers, stands without merit, since such markers are already available.

We urge Iams to bow out gracefully (and/or amend the research protocol to reflect viable non-animal alternatives such as bioartificial muscle technology) to minimize any potential damage this study has done and will do to Iams’ reputation. The honest truth is that consumers will not look favorably upon a company that willfully induces muscle atrophy in animals, especially considering the fact that Iams has been made fully aware of non-animal alternatives (per our letter dated November 1, 2004). We await your response by the end of November 2004, and we hope that Iams realizes that it’s time to stop defending this completely indefensible experiment.

Sincere regards,

A handwritten signature in black ink, appearing to read "Shalin D. Gala", written over a horizontal line.

Shalin Gala, Research Associate
Research & Investigations Department

cc: Mary Beth Sweetland