XIII. Appendix C. Public Comments and Response
(presented here exactly as submitted)

Status: U
From: linda.meyer@cp.Novartis.com
To: rg30@cornell.edu (Renu Gandhi)
Subject: Diazinon Breast Cancer Risk Evaluation
Date: Mon, 26 Apr 1999 15:15:22 +0200
MIME-Version: 1.0

Dear Dr. Gandhi,

Thank you very much for providing a copy of your draft document "Pesticides and Breast Cancer Risk, An Evaluation of Diazinon" to Darrell Sumner. Darrell was kind enough to forward it to me.

I believe the evaluation is well done and accurately reflects the conclusions that can be drawn based on available data. However, I would offer two comments for your consideration:

On page 2, in the section entitled "Does diazinon cause other types of cancer in laboratory animals?", a statement is made regarding the results of a long term study in rats in which an increased number of males in a diazinon treated group showed an abnormal increased growth of some cells in the pancreas. While it is true that the incidence of focal islet cell hyperplasia in the pancreas was statistically increased in males at the highest dose level in the referenced study, this is not a neoplastic change and there were no increased incidences of pancreatic tumors at any dose level. I recommend adding clarification to avoid the potential for confusion and misinterpretation. Perhaps a modification to the sentence as follows:

"In one study, groups of male rats that were fed diazinon over long periods of time had an abnormal increased growth of some cells in the pancreas more often than treated rats, however, incidences of pancreatic tumors were not increased by diazinon treatment."

In this same section, it is recommended that diazinon's effects on the pancreas be further investigated. I would like to point out that the effects of diazinon on the pancreas have, in fact, been investigated. Following is a brief summary of some studies (references follow) investigating the mechanisms for diazinon's pancreatic effects. I provide this just in case you do not already have this information.

The effects of diazinon on the pancreas of dogs, cats and Guinea pigs have been studied. Diazinon has been reported to cause acute pancreatitis in dogs, but not cats. The inhibition of the pancreatic tissue-fixed butyrylcholinesterase (BuChE) , which is present in dogs but not in cats, is proposed as the mechanism for inducing the observed pancreatic effects (Frick, T. W. et al, 1987). A few cases of human pancreatitis as a complication of acetylcholinesterase intoxication are reported in the literature. The pancreatitis could result from ductal obstruction and exocrine stimulation following cholinesterase inhibition. In one of the cases, ischemic impairment of the pancreas due to a cardiopulmonary arrest may have been a strong contributing factor to the pancreatic effects (Dresel, T. D., et al, 1979). In both dogs and humans, the pancreatitis observed following diazinon poisoning is of a transient nature (Dagli, A. J. et al., 1981; Weizman, Z. and Sofer, S., 1992). Acute pancreatitis as a consequence of anticholinesterase intoxication is a rare event following acute overexposure. Its occurrence is always associated with distinct symptoms of cholinesterase inhibition and is transient in nature.

Sincerely,

Linda S. Meyer, Ph.D.
Staff Toxicologist

linda.meyer@cp.Novartis.com,5/5/99 12:39 PM -0400,Re: Diazinon Breast Canc 1

To: linda.meyer@cp.Novartis.com
From: Renu Gandhi <rg30@cornell.edu>
Subject: Re: Diazinon Breast Cancer Risk Evaluation
Cc: sms31@cornell.edu
Bcc:
X-Attachments:

Dear Dr. Meyer,

Thank you for your comments on the draft Fact sheet on diazinon.

I reviewed again the animal study that had led me to make the remark on hyperplasia: Kirchner et al., 1991. The low and variable survival of the rats (as low as 30 to 35% in some groups) in the study, does not allow one to exclude the possibility that the pancreatic hyperplasia may have been pre-neoplastic. The incidence pattern of this disease in female rats was not available to me, but in males, all the treated groups had increased incidence compared to vehicle-fed controls, the increase being significant at the highest dose. Further, it is not sufficient to study the pancreatic hyperplasia effect for just its potential to transform into neoplastic tumors, but also for the exocrine and endocrine disruptions that are caused by the hyperplasia. Secondary exocrine and endocrine effects resulting from pancreatic toxicity of diazinon have not been followed. In other words, the pancreatitis attack may be reversible, but do all endocrine/exocrine secretions of the pancreas recover completely?

Our Critical Evaluation report of diazinon will be posted at our web site http://www.cfe.cornell.edu/bcerf/default.t for public comment in a few weeks. If you like, I can attach your comments to the technical report on diazinon as public comments received.

Thank you, once again!

Renu Gandhi