UNITED STATES GOVERNMENT

Memorandum

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
FOOD AND DRUG ADMINISTRATION

TO : Dr. Herbert Blumenthal
Chief, Petitions Review Branch, S-990

DATE: June 30, 1967

FROM : Dr. M. Adrian Gross
Acting Chief, Pathology Branch, S-980

SUBJECT : Pesticide Petition PP7F0599
Daconil 2787

Diamond Alkali Co.
Painsville, Ohio
(AF 25-202)

Hazleton Laboratories
Falls Church, Virginia
(AF 1-608)

At your request the Hazleton Laboratories slides on the 2 year dog livers were examined.

To minimize subjective bias, the examination and scoring was made without consideration of the identity of each animal and the following are the results:

Hepatic parenchymal degeneration of a central acinar type

Control-males	8381	- absent
	*8383	- absent
	8417	- minimal
-females	8421	- minimal
	8427	- absent
	8443	- absent
0.15% - males (low level)	8385	- absent
	8409	- moderate
	8411	- moderate to severe
- females	8403	- slight to moderate
	8423	- slight
	8441	- minimal

* the slide on this animal was (erroneously?) marked 8583.

A comparison of these scores with the impressions of the petitioner's pathologist reveals some discrepancies for individual animals; this could be accounted for by the fact that I have addressed myself principally to changes of a degenerative type--the ones most likely to

be caused by a chemical agent--and to ignore the inflammatory lesions which are probably due to other causes. Even so, the overall conclusion reached by Hazleton is quite similar to the one that I have made, namely that a higher proportion of dogs at the low level presented microscopic changes in the liver than the control animals did and the severity of these changes were, on the average, somewhat increased in the former group.

What is the significance of this lesion?

The answer can be given in several ways depending on one's point of view:

a) From the clinical point of view (the well-being of the animals themselves) it is clear that none of these lesions, and even more severe ones, would have any appreciable functional effect on the liver or on any other tissue.

b) From a pathology point of view, it is noteworthy that this type of lesion is at an initial stage of development which is reassuring for a 2-year study. At higher levels more advanced changes, including fibrosis, were observed which may mean one of two things: 1) the course of the pathologic process at the low level is identical to that observed at the higher ones but its latency is more prolonged or 2) the essential pathologic process operating at the high level has been arrested and limited to a preliminary stage at the low level. Obviously alternative (2) is preferable to (1) but there is no rational choice between the two.

c) From a toxicology point of view--has the agent itself caused these changes?--is the question one really wants to ask but, unfortunately, this cannot be answered except indirectly. The distribution of lesions of different degrees of severity among the two groups was such that saying that the agent had a slight effect on the liver carries a smaller risk of being false than a proposition that no effect was present at the low level. It is clear from the petition that this is the conclusion also reached by Hazleton and that they were hoping that we may bail them out of their problem by stating that the effect is of a negligible biological significance.

I would suggest here that it would be rash for us to do so simply due to the fact that we do not know the relative susceptibility of humans and dogs to this agent.

Perhaps someone may wish to obtain other and more expert consultation on this problem, but my view is that the only "experts" one is likely to round up will address themselves chiefly to points (a) and (b) above, the first which I have conceded and the second which I have partly conceded. Alas, there are no experts on point (c) who may give us the benefit of any additional experience we do not have here.

In the 2-year rat study it is noted that beginning at week 5 both the middle and the high level were discontinued; the middle one was subsequently restored gradually but the high level was not continued even at a reduced rate after week 16. At the middle level starting at week 46 only 8 animals/sex were continued on the diet plus the agent without additional protein and fat fortification. No information is given in the report as to which individual animals (for which pathology and other data are presented) where in what "dietary" group, and without this information I find it impossible to evaluate the safety of this agent. I will point out certain problems for the lowest level tried:

a) decreased survival for males
b) significantly decreased protein bound iodine for both sexes at 12 months, to some extent persisting to 24 months
c) grossly discolored and enlarged kidneys (greater frequency at higher levels)
d) gross alimentary tract changes
e) microscopic changes in the stomach and kidneys of both sexes and in the liver of females only
f) decreased body weight particularly for males

The most important histopathologic changes noted at 2 years in the low level animals can be listed as follows:

liver - parenchymal irregularity (more frequent in females).
kidney - tubular pigment deposition in males;
glomerulosclerosis in both sexes;
tubular hyperplasia in females;
tubular hypertrophy in both sexes;
capsular epithelial hyperplasia in both sexes;
focal epithelial hyperplasia in males.

In this connection it is worth mentioning that the dogs at the low level also had problems with glomerulosclerosis which was described as "moderate" for 2 animals (8409 and 8423) and without an adjective for a third (8411)

while three animals were classed as "negative." In the control group only two animals (8443 and 8421) were described as manifesting merely "slight" glomerulosclerosis while 4 were classed as "negative." At higher levels both the incidence and severity of this lesion increased.

In view of all this I find it difficult to state that the low level tried can be regarded as a "no effect" level.

cc S-1
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Gross

MAG:vo