COMPANY CORRESPONDENCE

TO DIV: Industrial Chemicals

FROM DIV: Industrial Chemicals

LOCATION: Morristown

LOCATION: Buffalo Dye Plant

ATT'N OF: Dr. W. Knapp

DATE: March 5, 1968

SUBJECT: PRODUCT TOXICITY
FDA ADVISORY COMMITTEE
MCA - FD&C CHEMICALS COMMITTEE

1. Please refer to Mr. Hoover's letter of February 29, 1968, referring to General Decker's letter of February 28, 1968 to Dr. Norton Nelson, Chairman FDA Advisory Committee.

2. It seems to me that there is one important area of omission in the MCA position statement. Not only should food chemicals be tested by ingestion but there should be a reasonable relationship between the dose level used in testing and the probable level of ingestion by man.

3. There are at least two reasons for keeping the dose/use level ratio within bounds. In the first place, feeding toxic chemicals at a level high in relation to the LD_{50} merely determines the carcinogenicity in debilitated or over-stimulated animals. In such cases, both the qualitative yield and the quantitative pattern of tumors can be distorted and misleading. Secondly, metabolism is not the same at high dose levels as at low levels. It is entirely possible that proximate carcinogens may be synthesized at high dose levels and not at low levels.

4. An illustration is the work on ortho tolidine reported by Pliss (Gigiena Truda i Prof. Zabolevaniya 9, No. 7, 18-22 (1965). In his experiments he found the LD_{100} to be no greater than 60mg/rat (100-130g). He still found mortality in 2-3 weeks at a dose of 30 mg so he settled on 20 mg/rat, once weekly for 13 months! And this by subcutaneous injection. He found lots of tumors in lots of organs and he concluded that o-tolidine is an active carcinogen only after metabolism and inferior (sic!) to 3,3' dichlorobenzidine. This is the type of data that leads some authorities to urge strict controls over tolidine and dichlorobenzidine.

5. Consider Pliss' study of dianisidine. He reports his rats were emaciated within a month on a thrice weekly dose of 30 mg/rat via gastic tube. After cutting the frequency in half, they still lost weight so he cut the dose to 15 mg/rat and administered a total of 2685 to 2835 mg/rat over 13 months!

From this feeding experiment, Pliss concludes that dianisidine is a weak carcinogen. I heartily agree on the adjective. After all, in terms of man, 2.75 grams/120 g rat/year is 1600 grams/man/year. Compare this with Dr. Beliczky's tentative threshold limit for such items of 0.075 mg/man/year. A ratio of 1,600,000/.075 or 21,000,000 to 1! Or in the case of the tolidine experiment, only 8,000,000 to 1.

6. I hope that the FDA Advisory Committee will bring some rule of reason into the picture. Their attitude in these matters is sure to have a heavy influence on the environmental health authorities who seem determined to impose stringent controls over industrial exposures.

K. H. Ferber
Technical Manager

KHF:ds

cc: Mr. J. Guelich
Mr. J. R. Horne
File (3)