CURRENT STATUS OF STUDIES ON DRIED FRUIT ADDITIVES

Dr. Floyd DeEds
Chief, Pharmacology Laboratory
Western Regional Research Laboratory[1]
Albany, California

The present high-moisture dried fruits are possible because of the use of small amounts of methyl formate, ethyl formate, ethylene oxide, and propylene oxide. Even smaller amounts of these compounds may remain in the treated fruits and in the case of ethylene oxide and propylene oxide small amounts of reaction products are formed. These residues and products are regarded as chemical additives under the interpretation of the Federal Food and Drug Act. Continued use of these small amounts of chemicals is dependent upon approval by the Federal Food and Drug Administration. This approval is dependent upon research which will supply adequate information regarding their lack of toxicity to the consumer of dried fruits. The present report concerns short-term toxicity tests which have been completed, or are in progress, and long-term toxicity tests on methyl formate and diethylene glycol.

On July 8, 1960, groups of weanling male and female rats were placed on long-term tests employing drinking water containing 0.0, 0.1, 0.5, and 2.5% methyl formate. Twenty-five rats of each sex were put on each dosage level. All dosage levels of methyl formate retarded growth of both sexes as compared with the controls due to a decrease in fluid intake. Comparable effects on growth were produced in other rats by comparable restriction of the fluid intake. After 125 days three rats given 2.5% methyl formate were returned to water free of methyl formate, and by the 210th day were nearly normal in weight. Rats receiving 2.5% methyl formate in drinking water and sacrificed after 125 days showed no evidence of injury other than that of dehydration and starvation. The rapid gain in weight strongly suggests that rats taken off 2.5% methyl formate and returned to straight water suffered no irreversible injury. Aside from effects on growth all rats appear normal at the present time. These results are shown graphically in Figures I and II.

On April 15, 1960, 25 weanling rats of each sex were placed on an adequate basal diet and on the same diet containing 0.04, 0.2, and 1.0% diethylene glycol. The general appearance and behavior of all these rats is normal. The growth rates of female rats on dietary levels of 0.04 and 0.2% diethylene glycol is practically the same as that of the controls, while that of rats on a dietary level of 1.0% is consistently and perhaps significantly less than that of the controls. The growth rate of male rats on a dietary level of 0.04% diethylene glycol is practically identical with that of the controls. The growth rate of male rats receiving 0.2% glycol is slightly less than that of the controls, and that of the rats receiving 1% glycol is below that of female rats on the same dosage. Figures III and IV show these results graphically.

On September 1, 1960, young beagle dogs were placed on dietary levels of 0.0, 0.04, 0.2, and 1.0% diethylene glycol. Three dogs of each sex are on each dosage level. All female dogs receiving diethylene glycol have grown as well as, or better than, the controls as shown in Figure V. At the present time the weights of the female dogs increase with increasing dosage of glycol. This is mentioned merely to emphasize that the female dogs do not show depression of growth. In the case of the male dogs there is a slight and consistent depression of growth rate on the 1.0% level of glycol. At present the weights of male dogs on 0.04 and 0.2% glycol are greater than that of the controls. Figure VI shows the growth curves for the male dogs.

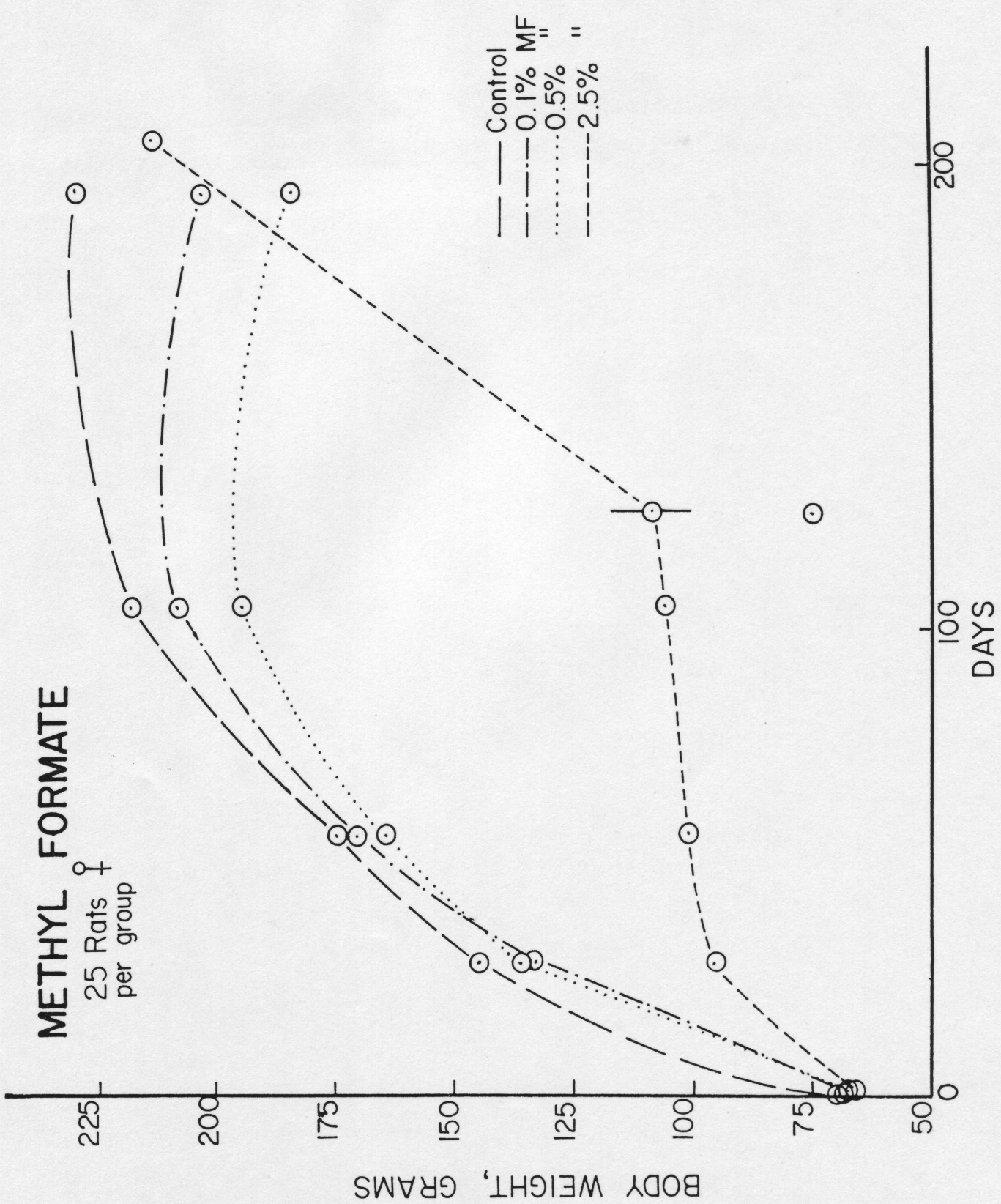
1. A laboratory of the Western Utilization Research and Development Division, Agricultural Research Service, U.S. Department of Agriculture.

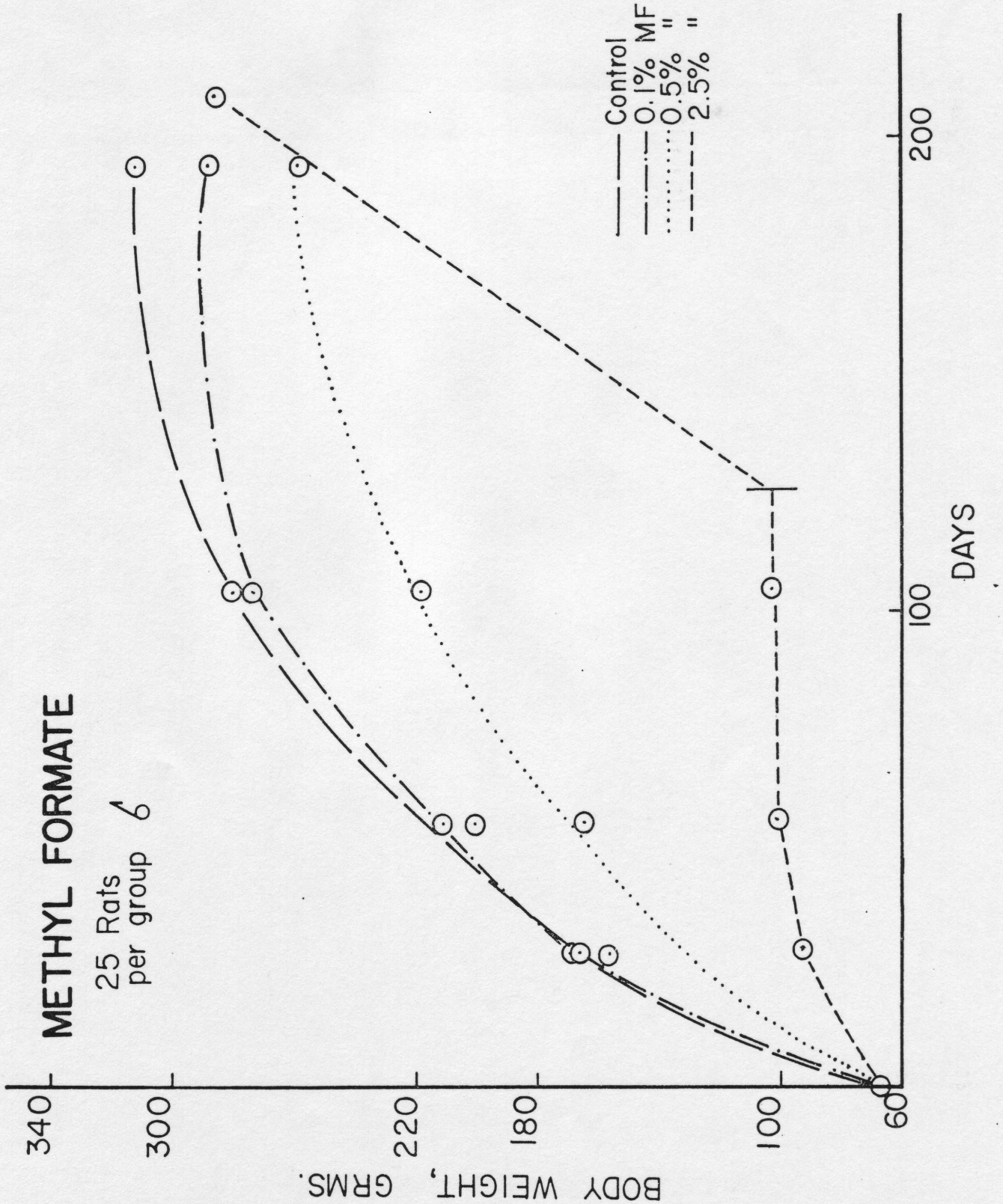
In addition to these long-term feeding tests several caloric value studies on reaction products have been completed or are in progress. A caloric value study is a short-term feeding test designed to determine whether or not a substance is absorbed from the digestive tract and whether or not it will supply energy required for growth. Reaction products of cellulose with ethylene oxide and with propylene oxide were prepared. The reaction products were fed to weanling rats and their utilization determined as judged by growth as compared with suitable controls. Neither cellulose reaction product was utilized as a source of energy, and the increased weight of the feces indicated complete lack of absorption. Glucose was reacted with propylene oxide in water at the average acidity existing in dried fruit. The reaction product after removal of unreacted glucose by fermentation was fed to weanling rats as in the case of the cellulose reaction products to determine its caloric value or utilization. The reaction product was as well utilized as glucose itself. Caloric value studies on the reaction product of glucose with ethylene oxide are in progress.

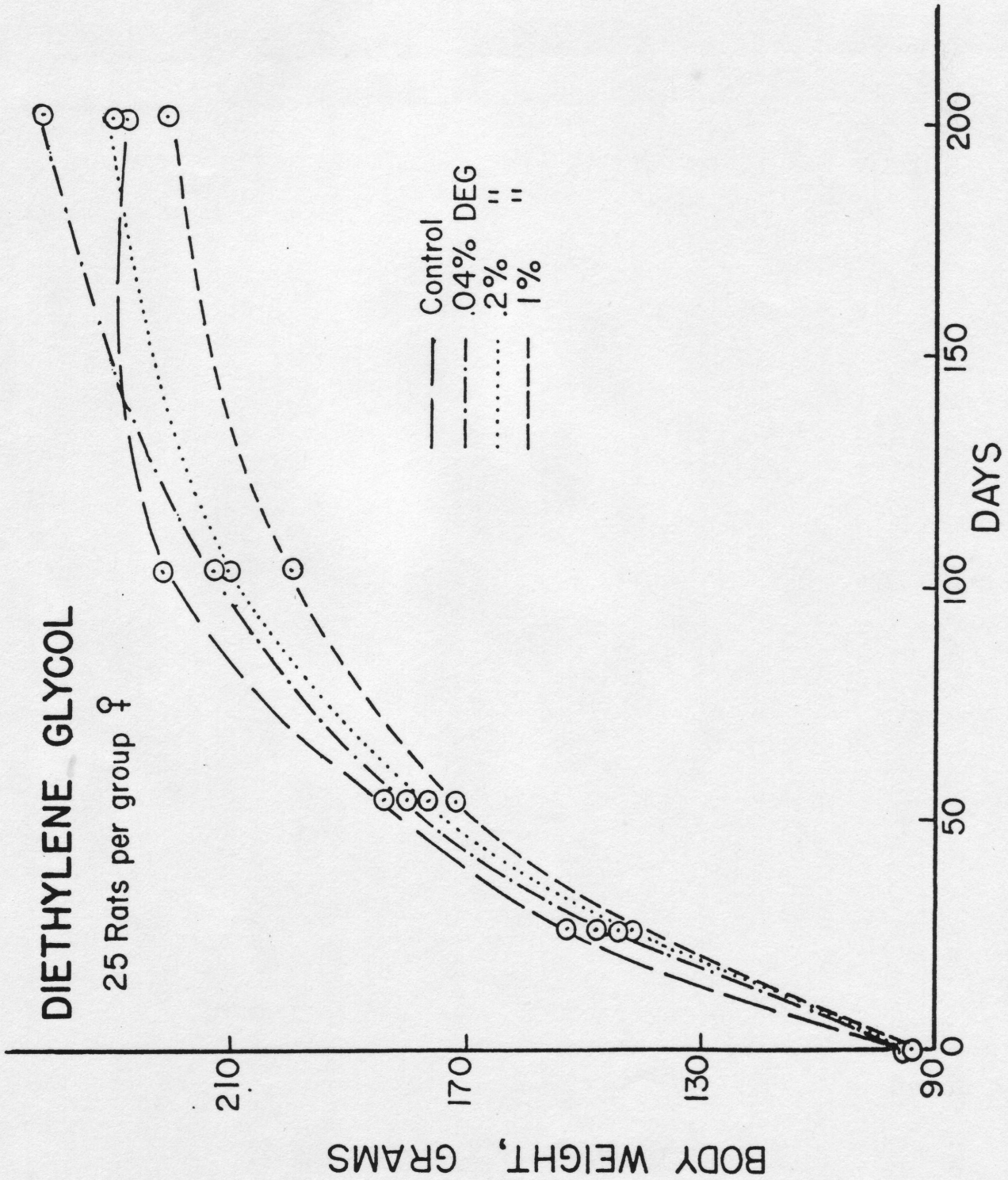
No mention has been made in this report of long-term feeding tests on propylene glycol comparable to those in progress on diethylene glycol. This is due to the fact that the Federal Food and Drug Administration is satisfied as to the safety of propylene glycol formed as a reaction product in dried fruits treated with propylene oxide. Diethylene and ethylene glycols formed in fruits treated with ethylene oxide are, however, regarded as potentially capable of producing bladder tumors. This is due to the fact that these two glycols are in part converted to oxalic acid in the animal body, and the calcium oxalate stones deposited in the bladder when high dietary levels of the glycols are present causes irritation resulting in tumors of the bladder. It is hoped that the present investigations will show that dietary levels of diethylene glycol, much greater than can be attained by eating ethylene oxide-treated dried fruit, will fail to produce bladder stones and therefore no bladder tumors will result.

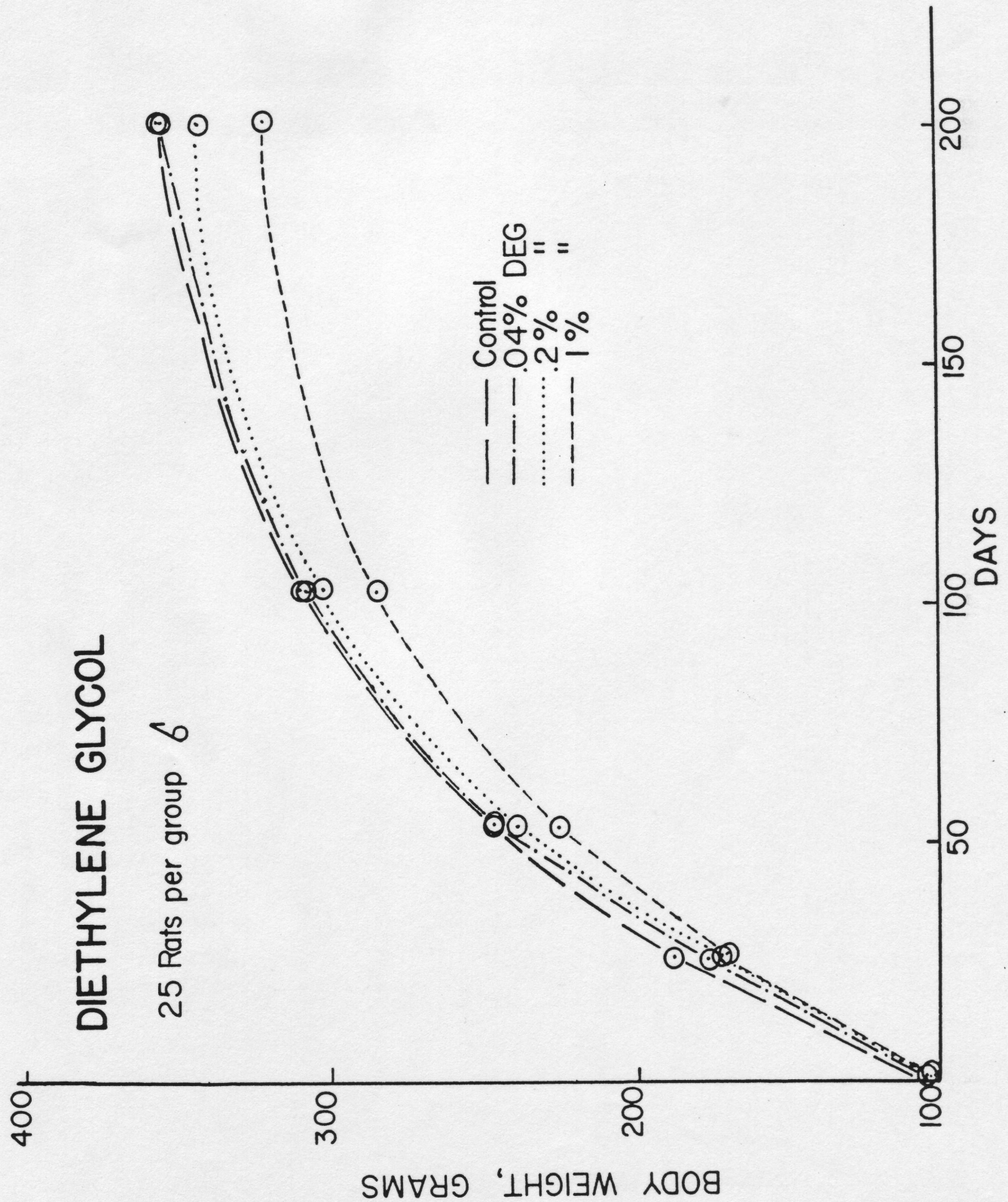
It should be pointed out that a favorable result on the diethylene glycol feeding tests will not necessarily assure a favorable ruling by the Food and Drug Administration for the use of ethylene oxide. The difficulty is due to the strict interpretation placed on the Delaney Clause of the amendment to the Federal Food and Drug Act. The practical effect of this interpretation is that if a compound is found to produce cancer in experimental animals or man, even though excessively high dosage is required, not even a trace of the compound will be permitted in a food. At the moment the decision is that there is no such thing as an ineffective dose of a cancer producing agent. It matters little if you and I disagree.

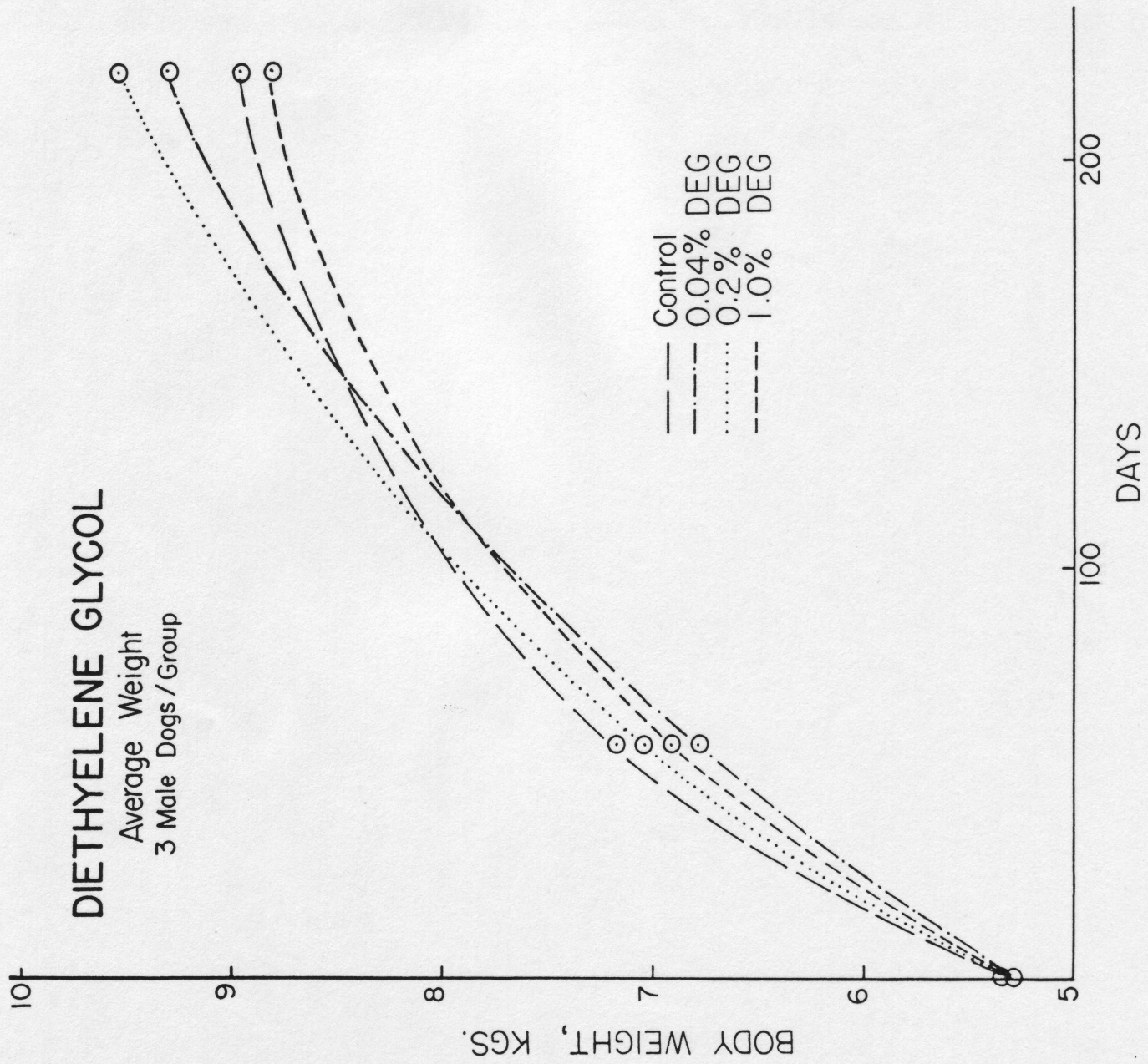
# # #

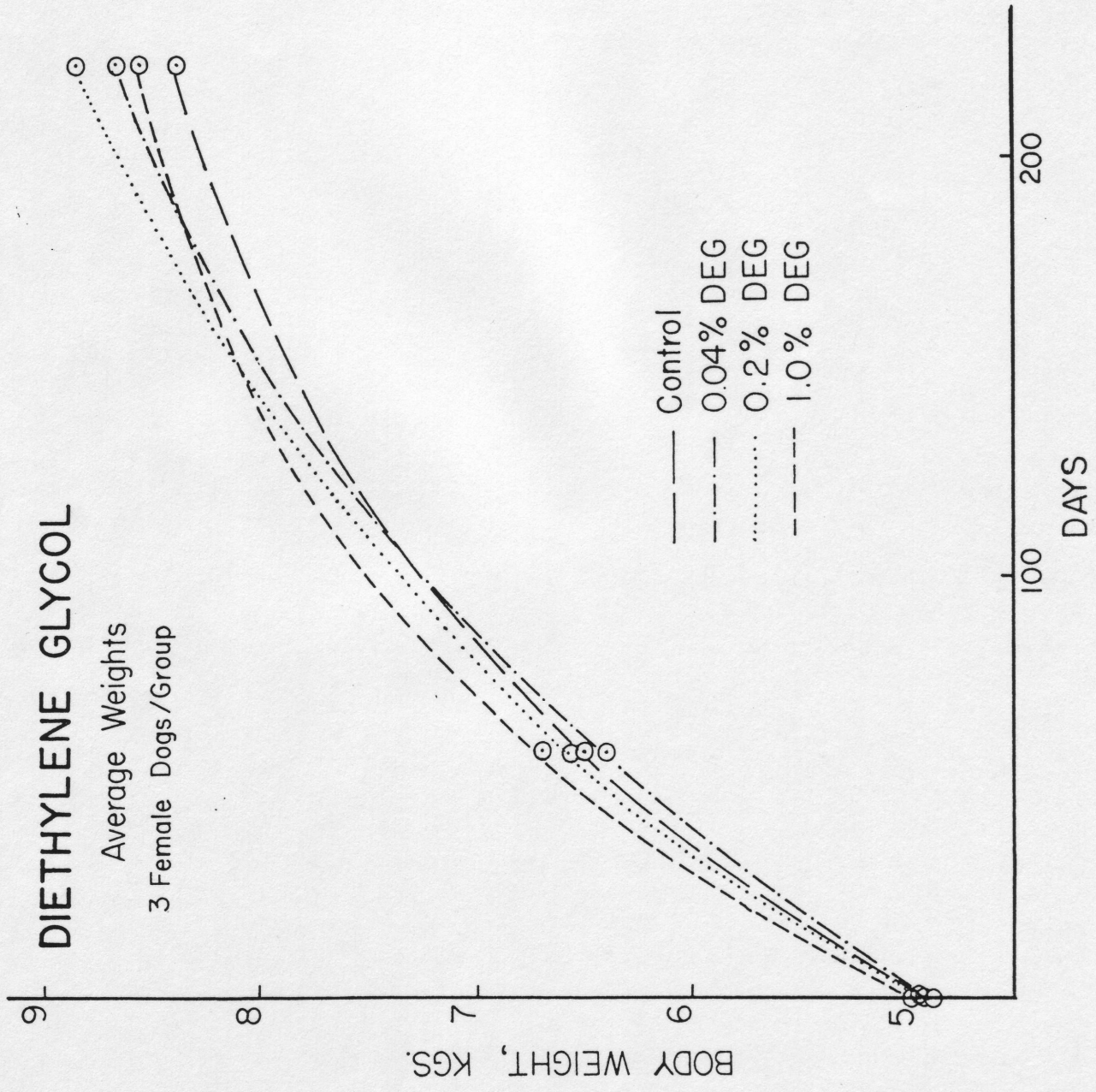

METHYL FORMATE
25 Rats ♀ ♂
per group
Control
0.1% MF
0.5% "
2.5% "
BODY WEIGHT, GRAMS
225
200
175
150
125
100
75
50
0
100
200
DAYS


METHYL FORMATE
25 Rats per group
Control
0.1% MF
0.5% "
2.5% "
BODY WEIGHT, GRMS.
340
300
220
180
100
60
100
200
DAYS


DIETHYLENE GLYCOL
25 Rats per group ♀
Control
.04% DEG
.2% "
1% "
BODY WEIGHT, GRAMS
210
170
130
90
0
50
100
150
200
DAYS


DIETHYLENE GLYCOL
25 Rats per group ♂
Control
.04% DEG
.2% "
1% "
BODY WEIGHT, GRAMS
400
300
200
100
50
100
150
200
DAYS


DIETHYELENE GLYCOL
Average Weight
3 Male Dogs / Group
BODY WEIGHT, KGS.
10
9
8
7
6
5
100
200
DAYS
Control
0.04% DEG
0.2% DEG
1.0% DEG


DIETHYLENE GLYCOL
Average Weights
3 Female Dogs/Group
BODY WEIGHT, KGS.
9
8
7
6
5
100
200
DAYS
Control
0.04% DEG
0.2% DEG
1.0% DEG