

# HOWARD UNIVERSITY

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SCHOOL OF MEDICINE  
DEPARTMENT OF PHARMACOLOGY

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Dear Dr. Lederberg:

I have followed your newspaper columns for some time and have found them refreshing for their sober and reasoned comments and for their absence of shrill invective. Consequently, I would like to take sober and reasoned issue with you on your remarks on the cancer clause in the Delaney Bill, of which you wrote in the guest editorial in C & EN 47:5:1969.

The basic premise of the Delaney Bill, widely used in pharmacology and toxicology, is the dose-response relationship, and therefore of a no-effect level for populations and individuals. In a population, this no-effect level may statistically be at a very low effect level; say 0.00005%. It is problematical that this low level effect would occur or be detected. Among other things the small number of susceptible individuals could well have been eliminated for other reasons. It is just as reasonable to expect this as to expect the complete carcinogenic effect in 100 individuals in a population of 200 million. More likely, the hazards of life would have eliminated some significant fraction of the susceptible individuals, and considerably less than 100 would have been affected; but of course, to each of the few individuals, it would have been extremely important. But the hazard to one or a few individuals in an entire population must be considered in the total context of all other hazards. Is liver damage, kidney damage or nerve fibre demyelination less undesirable than cancer induction? Tolerances for food additives and pesticides based on no-effect levels, and a safety factor, are established for many substances which cause such damage. These no-effect and safety levels may actually be greater than the 0.00005% level of which we spoke. The law says that the use level should be at the no-effect level and a safety factor. In this context, the cancer clause is irrational and the bill should be amended to place carcinogenic substances in the same category with other pharmacologically active substances, or to ban all such substances as food additives regardless of the level at which toxicity may occur. The latter occurred before the passage of the Delaney Amendment to the Food and Drug Act.

Whether the carcinogenic ED50 for the cyclamates was 50 times the use dose is really not the basic issue. The basic issue is whether the tolerance which is granted is rationally determined and whether it represents the most desirable allowable level of use. It has been common practice in the Food and Drug Administration to set the tolerances for food additives and pesticides at the no-effect level times an arbitrary safety factor of 100 (2 logs). Recently a 2000 times safety factor has been under discussion. Regardless of the figure, 100 or 2000, the use of an arbitrary factor is wrong. Consider two substances, carcinogenic or otherwise, but with the same ED50. The slope of the regression of one of these is 5, and of the other, 0.0001. One tenth the ED50 (1 log) of the first would affect 8.5% of the population. The same fractional dose of the second would affect 45%. In one instance 100X the no-effect level would be quite safe; in the other, it would be anything but safe.

It is in the disregard of such differences that the greatest danger lies.

In the case of cyclamates, cancers have been induced at doses of only 50X greater than use levels (1.7 logs), and I have been told that statistically significant increases in cancer have been found at lower doses and at locations other than the bladder. The case is strong for the discontinuance of the use of cyclamates, since the assumption is that carcinogenesis is equal among the mammalian species (which, of course, may not be true).

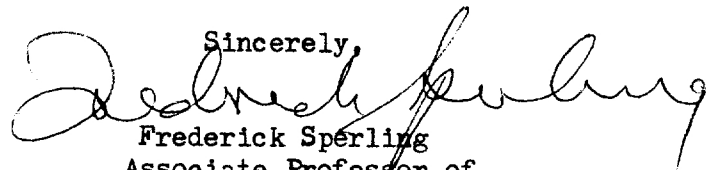
It would be better to amend the cancer clause in the Delaney Bill. It would also be better to eliminate the GRAS list. In its place I would suggest a reimposition of the "prior sanctions" category, with no time limit, such as the original category had. In this category, those compounds with a long history of use, or those which might be used with no apparent hazard at any level, would be subject for study by producers if the FDA found any reasonable cause for such study.

Some of the answers must be found in better legislation and in rational administration of such legislation.. And it is such as you, who must lead the way.

If this letter is too long, accept my apologies. It has been pared considerably from what I originally wrote.

My best wishes of the Season.

Sincerely,



Frederick Sperling  
Associate Professor of  
Pharmacology