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life or limb to gain access to areas that are hidden by moving equipment.

Federal inspectors are covered by compensation for injuries suffered on the job. Most mills and elevators have public liability insurance which would protect any visitor who was injured on the premises but it may not cover inspectors who are injured on official inspections. Litigation is now in progress in Oklahoma to determine whether the insurance company or the elevator is liable for injuries to an inspector on official business.

QUARTERLY REPORT TO THE EDITOR ON TOPICS OF CURRENT INTEREST

100-FOLD MARGIN OF SAFETY

In attempts to predict the safety of a proposed food additive to humans in terms of toxicity in animals, the statement has been made that the additive should have at least a 100-fold margin of safety. The term "100-fold margin of safety" signifies that the chemical additive should not occur in the total human diet in a quantity greater than \( \frac{1}{1000} \) of the amount that is a maximum safe dosage in long-term animal experiments. For ease of interpretation the total amount of the chemical in the diet of man and animals can be expressed in parts per million. If the assumption is made that the experimental animal reacts just as man, then a "safe dose" in the sense ordinarily used in discussions of chronic toxicity is that dose just short of causing an observable effect. Good pharmacological judgment dictates that there shall be a clear distinction between a safe dose and a toxic dose.

Why a factor of safety?

1. Animals for the most part are more resistant to toxic chemicals than man. This can be illustrated for two familiar substances for which some chronic toxicity data are available for two commonly employed laboratory animals and for man. Man can ingest 1 part per million of fluorine in his daily diet without harmful effects, whereas the rat can tolerate about 10 parts per million. In experiments on subacute toxicity man begins to show signs of intolerance to arsenic at about 30 parts per million in the diet, whereas the dog can tolerate 127 parts
per million. In other words, man is about 10 times as sensitive to poisons as the rat, and somewhat more than 4 times as sensitive as the dog.

2. There is considerable variation in susceptibility among animal species. This susceptibility changes from one substance to another, but in general rats are less susceptible to toxic substances than dogs and slightly more susceptible than mice.

3. There is variation in susceptibility within the different strains of the same species, with age within the same strain, and within different animals of the same strain, age and sex. Since the human population as a whole is heterogeneous, the factors influencing susceptibility are of particular importance in assessing the human hazards.

4. In experimental work the animals employed are chosen from a healthy stock and are kept under controlled conditions, whereas humans vary greatly in state of health, type of diet, and all conceivable conditions of existence. Sickness increases susceptibility to toxic substances. It has been estimated that a sick individual may be as much as 10 times more susceptible to toxic substances than an individual in good health. Dietary inadequacies also influence the effects of noxious substances as does physical stress—heat and cold. Thus, allowance must be made for these influencing factors as well as for the healthy average individual on an adequate diet.

5. In the over-all consideration of the safety of a material in human use all of the auxiliary factors that make up the diet characteristic of the human must be taken into account. The proposed additive will be only one of a number of other substances that may be unintentionally or unavoidably added to foods tending to increase the total strain on the body’s catabolic mechanisms. It has been shown that the effect of feeding a combination of certain insecticides in the same diet is greater than the effect of any one in the group. Even a history of long usage in man is not adequate proof of safety. Laboratory re-evaluation of such substances as lithium chloride, a salt substitute, dulcin, a synthetic sweetening agent, and coumarin, a flavor, has shown these materials to be unsuitable as additives to the human dietary.

The “100-fold margin of safety” is a good target but not an absolute yardstick as a measure of safety. There are no scientific
or mathematical means by which we can arrive at an absolute value. However, this factor of 100 appears to be high enough to reduce the hazard of food additives to a minimum and at the same time low enough to allow the use of some chemicals which are necessary in food production or processing. The application of simple statistical rules indicates that the probability of human injury decreases with each increase of the margin of safety.

Since man can seldom be used as an experimental subject, reliance for the evaluation of the toxicity of a substance must ordinarily be placed upon studies in laboratory animals. Even then it cannot be said for certain that lack of toxicity in animals will necessarily forecast what may occur in man. However, the selection of the 100-fold margin of safety serves as a reasonable safeguard to minimize the danger.

A. J. L.
O. G. F.

NEWS ITEM

A. O. A. C. CONFERENCE

A total registration of 608 at the sixty-seventh annual meeting of the Association of Official Agricultural chemists held at the Shoreham Hotel in Washington, D.C., October 12, 13 and 14 was greater than that of any previous meeting. Registrants from 38 states, Canada, Brazil, and Egypt were in attendance. The annual banquet of the Association attended by 181 members and guests was addressed by Mr. Parke M. Banta, General Counsel of the Department of Health, Education, and Welfare, on the subject of Federal and State cooperation in the regulatory field. Dr. Hugh Magee, Senior Medical Officer of the British Ministry of Health in charge of Nutrition, who is visiting research laboratories in this country also spoke briefly on his work in the field of nutrition. The women chemists of the Association held a luncheon at which Mrs. Harvey W. Wiley was the honored guest. Mrs. Wiley reviewed the relationship between the Association and Dr. Wiley. The annual address of the President of the Association was delivered by Dr. Harry J. Fisher. Dr. Fisher traced the contributions that his organization, the Connecticut