LETTERS

Dioxin Studies

In reference to the article, "Agent Orange furor continues to build" by Constance Holden (News and Comment, 24 Aug., p. 770), I note that no mention is made of long-term studies of the effects of exposure to dioxin on human health that are being conducted by the National Institute for Occupational Safety and Health (NIOSH).

NIOSH, with cooperation from the chemical industry, major unions, and the Department of Defense, is compiling a registry of the population of chemical workers in the United States who have had documented exposure to the constituents of Agent Orange, such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), either in the manufacture of 2,4,5-trichlorophenol (2,4,5-T) and other herbicides or in industrial accidents. Once this registry has been developed, NIOSH plans to evaluate trends in mortality of the exposed workers and, if the data permit, will consider conducting morbidity and reproductive studies. Because the manufacture of TCDD-contaminated herbicides began in this country as long ago as the mid-1940's, this registry of several thousand exposed workers should provide information on the effects of dioxin exposure that will be relevant to the present and future concerns of Vietnam veterans.

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Nitrate and Nitrite: Origin in Humans

The report by Witter *et al.* (27 Apr., p. 411) on the use of labeled nitrate ($^{13}NO_3^-$) to investigate nitrate pharmacokinetics in humans and the rat represents an important contribution to the literature, and directly substantiates several facts that were previously known only through indirect measurements. The most relevant of these is that nitrate is absorbed primarily in the upper portion of the small intestine, and that small quantities can reach the lower intestinal tract via the intestinal tube or by reverse diffusion from blood. The significance of these new findings to the interpretation of our earlier report (30 June 1978, p. 1487) on excess nitrate synthesis in humans, and to our hypothesis of intestinal heterotrophic nitrification requires further comment. We believe these new findings support our hypothesis and demonstrate that reverse diffusion could not account for the concentrations of nitrate and nitrite in urinary, ileal, and fecal fluids.

The elimination of nitrate from the body via excretion in urine has been followed in our laboratory in young and old individuals on a variety of diets over periods of 1 month or longer. We are currently working on a study in which 24-hour urine samples have been collected for a consecutive period of 80 days. The most characteristic feature of urinary excretion of nitrate by individuals on our formula diets is the extreme variability from day to day. The daily nitrate intake, as we reported, ranges from approximately 75 to 150 micromoles, while the output exceeds the input by factors of 2 to 60. Over a period of 80 days, the average excess nitrate excretion of individuals on a soy diet is greater than 5 grams. Verification of our observations has recently appeared (*1*) and has also been communicated in correspondence (*2*).

Our studies, and those of others who have conducted careful experiments on nitrate metabolism, indicate the following highly simplified picture: nitrate clearance from blood after an oral dose involves a distribution phase of 2 to 5 hours to peak concentration in urine and saliva, and a clearance phase with a half-life of approximately 8 hours (*3*). It is also well known that nitrate rapidly equilibrates with extracellular water (*4*). Therefore, if one assumes no further entry of nitrate, the body could clear its pool in approximately 48 hours, independent of the initial concentration of the pool, since clearance is first-order in concentration of nitrate. This is, in fact, the observed result of the studies previously cited and is also verified by our unpublished observations of blood nitrate concentrations in fasting individuals.

While the ^{13}N technique would appear to be extremely valuable for short-term distribution studies, the short half-life of ^{13}N limits its experimental use to time periods that are shorter than the distribution phase of nitrate given orally in vegetables or vegetable juices. Another deficiency is the lack of resolution of the method, which did not permit the experimenters to distinguish, for example, intestinal contents from intestinal wall. A third deficiency, as noted by the authors, is the lack of ability to distinguish between nitrate and its reaction products. This is a serious difficulty in the inter-