

This Week's Citation Classic®

Mirvish S S. Formation of *N*-nitroso compounds: chemistry, kinetics, and *in vivo* occurrence. *Toxicol. Appl. Pharmacol.* 31:325-51, 1975.
[Eppley Institute for Research in Cancer, University of Nebraska Medical Center, Omaha, NE]

This article reviewed the formation of nitrosamines and nitrosamides (*N*-nitroso compounds) from nitrite and amines or amides, with emphasis on chemical kinetics, inhibition by vitamin C, and *in vivo* occurrence. The amines and amides included drugs, pesticides, and food components. [The *SCI*® indicates that this paper has been cited in over 380 publications, making it the most-cited paper for this journal.]

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April 22, 1987

In 1967 I began research on *N*-nitroso compounds (NOC) at the Weizmann Institute of Science in Israel. To evaluate amine nitrosation *in vivo* (which had just been demonstrated by J. Sander¹ in the Federal Republic of Germany) and in foods, I examined the kinetics of acid-catalyzed dimethylamine (DMA) nitrosation, to give dimethylnitrosamine (DMN), following studies by J.H. Ridd in London. In 1969 I joined the Eppley Institute, which had an active group working on NOC. Since the rate of amine nitrosation depends on the proportion of reactive non-ionized amine at acidic pH, amines that are weaker bases than DMA should be nitrosated much more readily than DMA. Accordingly, we studied the nitrosation kinetics for secondary amines of varying basicity and for *N*-substituted amides. Also, M. Greenblatt and I induced tumors in mice by feeding them nitrite with amines or amides.

During the early 1970s, the late Leo Friedman of the Food and Drug Administration regularly assembled the scientists working on NOC, mainly to discuss the nitrosamines discovered in fried bacon. These gatherings and the International Agency for Research on Cancer meetings on NOC helped to direct our research in rather practical directions. In 1972 we found that vitamin C inhibited nitrosation by reducing nitrite to nitric oxide. We discovered this when our director, P. Shubik, asked us to check a report by W. Lijinsky that tetracycline reacts with nitrite to yield DMN. We could not initially confirm the report and traced this to vitamin C in our drug sample. Increased amounts of vitamin C are now added to bacon to lower nitrosamine formation.

In 1974 I reviewed NOC formation at a Society of Toxicology symposium. The written account grew to become a full review, including unpublished studies from my laboratory by Jim Sams, Steve Arnold, and Cecilia Chu. In 1981 the subject of NOC was updated in a monograph.²

The University of Nebraska gave me its Award for Outstanding Research and Creativity in 1985 based mainly on the vitamin C work. I recently reviewed the possible role of NOC in the etiology of a human cancer³ and the actions of dietary vitamin C.⁴

I believe my 1975 paper is quoted mainly because of the tables it includes that list kinetic rate constants for the nitrosation of 15 amines and 21 amides, which are used to help evaluate whether specific chemicals are likely to form NOC.

1. Sander J, Schweinsberg F & Menz H P. Untersuchungen über die Entstehung cancerogener Nitrosamine im Magen (Studies on formation of carcinogenic nitrosamines in the stomach). *Hoppe-Seyler's Z. Physiol. Chem.* 349:1691-7, 1968. (Cited 160 times.)
2. Committee on Nitrite and Alternative Curing Agents in Food, Assembly of Life Sciences. *The health effects of nitrate, nitrite and N-nitroso compounds: part 1 of a 2-part study.* Washington, DC: National Academy Press, 1981. 529 p.
3. Mirvish S S. The etiology of gastric cancer: intragastric nitrosamide formation and other theories. *J. Nat. Cancer Inst.* 71:629-47, 1983.
4. -----, Effects of vitamins C and E on *N*-nitroso compound formation, carcinogenesis, and cancer. *Cancer* 58:1842-50, 1986.