M. T. Hazee-Hagelstein, W. M. G. Tunbridge, *J. Reprod. Fertil. Suppl.* **26**, 123 (1979).
12. K. Ramasharma and M. R. Sairam, *Ann. N.Y. Acad. Sci.* **383**, 307 (1982).
13. _____, M. R. Ranganathan, *Acta Endocrinol. (Copenhagen)* **98**, 496 (1981).
14. N. G. Seidah, J. Rochemont, J. Hamelin, M. Lis, M. Chrétien, *J. Biol. Chem.* **256**, 7977 (1981).
15. M. R. Sairam, in *Hormonal Proteins and Peptides: Gonadotropins*, C. H. Li, Ed. (Academic Press, New York, 1983), vol. 11, pp. 1–79.
16. A. V. Schally, *Science* **202**, 18 (1978).
17. M. O. Dayhoff, *Protein Sequence Data Base, Update* (National Biomedical Research Foundation, Washington, D.C., 1983).
18. C. C. Q. Chin, J. M. Brenner, F. Wold, *J. Biol. Chem.* **256**, 1377 (1981).
19. M. J. Holland, J. P. Holland, G. P. Thill, K. A. Jackson, *ibid.*, p. 1385.
20. The existence of homology in structure as well as function among distinctly related eucaryotes has been reported; see L. T. Hunt and M. O. Dayhoff, in *Peptides: Structure and Biological Function*, E. Gross and J. Meinhofer, Eds. (Pierce Chemicals, Rockford, Ill., 1979), p. 757; M. O. Dayhoff, in *Atlas of Protein Sequence and Structure* (National Biomedical Research Foundation, Washington, D.C., 1978), vol. 5, suppl. 3; K. Lederis *et al.*, *Can. J. Biochem. Cell. Biol.* **61**, 602 (1983); K. C. Robbins, H. N. Antoniades, S. G. Bevare, N. W. Hunkapiller, S. A. Aaronson, *Nature (London)* **305**, 605 (1983).
21. The peptide corresponding to the 31-amino-acid sequence was synthesized by the solid-phase method. The purity of the synthetic peptide was established by HPLC and paper electrophoresis, and its amino acid composition was identical to the proposed sequence [R. B. Merrifield, *J. Am. Chem. Soc.* **85**, 2149 (1963); D. Yamashiro and C. H. Li, *ibid.* **100**, 5174 (1978); C. H. Li, D. Yamashiro, K. Ramasharma, M. R. Sairam, unpublished data].
22. Supported by the Ford Foundation and the Medical Research Council of Canada. We thank C. A. Paulsen, G. Bleau, R. Vauclair, and M. O. Dayhoff for their contributions, and C. Chagnon Labelle and R. Carrière for technical assistance.
* To whom correspondence should be directed.

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3. P. Honchar and W. Halperin, *Lancet* **1981-I**, 618 (1981); P. Honchar, M. Fingerhut, W. Halperin, in preparation.
4. W. Wagner, paper presented at the SOEH Conference, The Scientific and Social Response from Exposure to Dioxin and Related Materials (Society for Occupational and Environmental Health, Arlington, Va., December 1983). The Environmental Protection Agency, report was originally intended to be released in November 1983, but has not yet been released.
5. T. Sterling and A. Arundel, *NCAP News*, in press.
6. O. Axelson and L. Sundell, *Work Environ. Health* **11**, 21 (1974).
7. L. Hardell, M. Eriksson, P. Lenner, E. Lundgren, *Br. J. Cancer* **43**, 169 (1981).
8. Ton That Tung, *Chirurgie* **99**, 427 (1973).
9. A. Westing, Ed., *Proceedings, International Symposium on the Long-Term Consequences of Chemical Warfare in Vietnam* (Stockholm International Peace Research Institute, Stockholm, Sweden, 1983).
10. E. Silbergeld, paper presented at the SOEH Conference, The Scientific and Social Response from Exposure to Dioxin and Related Materials (Society for Occupational and Environmental Health, Arlington, Va., December 1983).

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Health Effects of Dioxin

The evidence of deleterious health consequences from the environmental use of substances containing 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) has appeared in a multitude of studies. Philip H. Abelson's editorial (*1*) on the dioxin issue is based on a number of misleading inaccuracies about this evidence.

First, the results of the accident at Seveso, Italy, are not limited to mild cases of chloracne, despite Abelson's statement that "No significant change was observed in the incidence of spontaneous abortions, congenital malformations, or postnatal development." The Seveso data (*2*) show a sharp increase in spontaneous abortions during the first trimester of 1977, followed by a slow decrease to 1976 levels and significant increases in risk of malformations. For example, there was a 100 percent increase in the rate of spina bifida, a 71 percent increase in the rate of neural tube defects, an elevenfold increase in hypospadias, and a 110 percent increase in polydactyly. A number of these malformations are frequently observed in animals exposed to TCDD. The Seveso data are still being analyzed for postnatal effects.

Second, the National Institute of Occupational Safety and Health (*3*) and recently the Environmental Protection Agency (*4*) followed workers exposed to TCDD in industrial accidents and found, in sharp disagreement with scientists who analyzed that data for industry, a multiple increase in soft tissue carcinomas and lymphomas.

Third, the question is not whether TCDD has to be ingested before it is toxic (obviously it has to make effective contact) but whether there is an effect from the presence of elevated environmental levels of TCDD, especially as a result of herbicide spraying (*5*). There is ample evidence that the latter is the case. Multiple studies by Swedish investigators, notably, Axelson and Sundell (*6*) and Hardell and Erikson and their colleagues (*7*) show an increase in soft tissue carcinomas in railway and forestry workers exposed to environmental TCDD. Observations from Vietnam (*8*) have reaffirmed increased liver cancer among populations exposed to Agent Orange during the Vietnam War (*8*). Spontaneous abortions, stillbirths, and malformations are still reported in these areas (*9*).

Fourth, it is misleading to stress the great variability of the median lethal dose (LD_{50}) when commenting on the value of animal experiments. It would be more accurate to point to the uniformly low effective doses for producing carcinogenic and teratogenic effects (*10*).

THEODOR D. STERLING
Faculty of Interdisciplinary Studies, Department of Computer Science, Simon Fraser University, Burnaby, British Columbia, Canada V5A 1S6

References and Notes

1. P. H. Abelson, *Science* **220**, 1337 (1983).
2. P. Bruzzi *et al.*, "Birth defects in TCDD polluted areas" (Provisional Report, Seveso Birth Defects Registry, Seveso, Italy, 1981); *Reporto Conclusino Sui Defetti Congeniti Ed Altri Esiti Sfavorevoli Di Gravidanza Relaveti Nella Popolazione Del L'Area Di Seveso Interasata Dall' Inquinamento Da TCDD IL 10.7.1976* (Registro Delle Malformazioni, Seveso, 28 June 1983).

Pro and con evidence and differing points of view on questions concerning the toxicity of dioxin are cited in a large number of articles and books. Three publications that contain a total of hundreds of references are

1) *Further Review of the Safety for Use in the U.K. of the Herbicide 2,4,5-T* from the Advisory Committee on Pesticides, London, December 1980;

2) *Agent Orange Dioxin—The Health Effects of "Agent Orange" and Polychlorinated Dioxin Contaminants*, a technical report prepared by the Council on Scientific Affairs of the Advisory Panel on Toxic Substances of the American Medical Association, Chicago, Illinois, October 1981; and

3) *Human and Environmental Risks of Chlorinated Dioxins and Related Compounds*, edited by Richard E. Tucker, Alvin L. Young, and Allan P. Gray (Plenum Press, New York, 1983).

As Sterling points out, a number of investigators have taken the position that TCDD has been a causative agent of soft tissue sarcomas. However, to other experts, the evidence is not compelling.

The Agent Orange report includes the following statement (p. 28): "While 2,4,5,-T and 2,4-D pesticides (phenoxy herbicides in Agent Orange) have been used in agriculture, forest management, and residential landscaping for over 30 years, there is still no conclusive evidence that they and/or TCDD (a contaminant of Agent Orange) are mutagenic, carcinogenic, or teratogenic in man, nor that they have caused reproductive difficulties in the human."

—PHILIP H. ABELSON

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