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This Week's Citation Classic®

Kimbrough R D & Gaines T B. Hexachlorophene effects on the rat brain: study of high doses by light and electron microscopy.
Arch. Environ. Health **23**:114-18, 1971.
[Food and Drug Admin., Div. Pesticide Chem. and Toxicol., Atlanta Toxicol. Br., Chamblee, GA]

Hexachlorophene [2,2'-methylene-bis (3,4,6-trichlorophenol)] was fed to rats at a daily dose of 25 mg/kg body weight per day. After two weeks, the rats developed leg weakness that progressed to paralysis. The brains of the dosed rats weighed significantly more than those of the controls. The brain lesion was cerebral edema (spongiform alteration) limited to the myelin sheaths. [The *SCI*® indicates that this paper has been cited in over 160 publications since 1971—one of the most-cited papers ever published in this journal.]

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While working for the US Food and Drug Administration (FDA), I became interested in compounds made from 2,4,5-trichlorophenol because of the possibility that these chemicals might be contaminated with 2,3,7,8-tetrachlorodibenzodioxin. Hexachlorophene was among the compounds made from 2,4,5-trichlorophenol. No toxic effects related to 2,3,7,8-tetrachlorodibenzodioxin were actually found. Instead, the neurotoxic effects of hexachlorophene were uncovered.

In 1968, the patent that Givaudan had on hexachlorophene expired and attempts were made by other industries to expand the use of hexachlorophene, including use on food crops. At that time, hexachlorophene was already extensively used in many cosmetics and as a germicide. It was particularly recommended for washing of infants in nurseries to prevent staphylococcus infections. One day, after the hexachlorophene study had begun, the supervisor of the animal caretakers, Richard Moore, walked into my office and informed me that rats dosed with hexachlorophene could not walk properly. The rats did indeed show weakness of their hindlegs that later progressed to paralysis. Careful examination of the brain revealed a spongiform alteration of the white matter that, on electron microscopic examination, was found to be due to splits in myelin sheaths. These splits had filled with fluid, resulting in vacuolation of the myelin sheaths. I recalled having read about such a brain lesion that had been caused by triethyltin. Such lesions in the white matter therefore could indeed be produced by chemicals. I concluded that hexachlorophene, which had been considered safe, caused a serious neurological effect in rats.

Could this brain lesion also be produced in other species by hexachlorophene? It was ultimately determined that the lesion could be produced in mice, dogs, monkeys, pigs, tadpoles, sheep, and rabbits and was also found in a retrospective study in premature infants that had been washed with hexachlorophene and had presumably died of other causes. Subsequently, a poisoning outbreak among babies in France was traced to hexachlorophene, and the brain lesion was observed there in the infants that died from hexachlorophene poisoning. All of these findings led to a great deal of controversy. Many meetings were held that, at times, resulted in heated discussions. Subsequently, hexachlorophene was made a prescription drug in the US by the FDA, and the American Academy of Pediatrics revised their recommendations for infant bathing.

The first journal I sent my manuscript to for publication did not accept it, claiming that the lesion was an artifact. Since then, it has been demonstrated by a number of leading neuropathologists that the lesion does indeed occur.[1-4] Much research has been done on the toxicity of hexachlorophene since the publication of the article cited above, but its mechanism of action is still not well understood. The problems uncovered with hexachlorophene generally led to concern in the FDA about dermal absorption of chemical substances and a review of that entire area. At the time the hexachlorophene brain lesion was recognized in rats, my coworkers and I, with the help of Lawrence Finberg, were able to show that body bathing of infants with hexachlorophene increased their hexachlorophene blood levels. Again we had difficulties publishing our results.[5]

I learned from this experience that in spite of all the controversy I faced, there are many extremely conscientious physicians and other scientists who evaluate new findings responsibly and, beyond all else, are concerned about public welfare.

1. **Kimbrough R D.** Hexachlorophene: toxicity and use as an antibacterial agent. (Hayes W J, ed.) *Essays in toxicology*. New York: Academic Press, 1976. Vol. 7. p. 99-120.
2. **Lampert P, O'Brien J & Garrett R.** Hexachlorophene encephalopathy. *Acta Neuropathol.* **23**:326-33, 1973. (Cited 75 times.)
3. **Mullick F G.** Hexachlorophene toxicity—human experience at the Armed Forces Institute of Pathology. *Pediatrics* **51**:395-9, 1973.
4. **Shuman R M, Leech R W & Alvord E C, Jr.** Neurotoxicity of hexachlorophene in the human: I. A clinicopathologic study of 248 children. *Pediatrics* **54**:689-95, 1974.
5. **Curley A, Hawk R E, Kimbrough R D, Nathenson G & Finberg L.** Dermal absorption of hexachlorophene in infants. *Lancet* **2**:296-7, 1971. (Cited 100 times.)