Contract No. V101(83)P-1138; Provides a brief review of occupational exposure of nurses to hexachlorophene.
ADDENDUM

LITERATURE REVIEW AND BIBLIOGRAPHY

DELIVERABLE A

SUBMITTED BY NEW ENGLAND RESEARCH INSTITUTE, INC.

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This addendum provides a brief review of an important occupational exposure for nurses - hexachlorophene - not included in the original review. This review should be included as Sub-section 5.1 A Exposure: Hexachlorophene, in Section 5. Nursing: Occupational Risks.

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5.1.A EXPOSURE: HEXACHLOROPHENE

Fingerhut et al. (1985) in an update of an earlier article present a status report on the NIOSH Occupational Dioxin Registry. This report indicates, clearly, that 2,3,7,8-TCDD (abbreviated to TCDD) is a contaminant in the process of manufacturing hexachlorophene as well as 2,4,5-T. Figure 1, reproduced from this report, summarizes the chemical process which produces 2,4,5-T, hexachlorophene and TCDD as a contaminant.

Hexachlorophene was used for many years as a cleansing and disinfecting agent, with nurses being a consistently exposed occupational group. This substance was used routinely by nurses all through the period of the Vietnam conflict, until the late 1970's, when it was gradually withdrawn from use.

Primarily used as a bacteriostatic agent, patients showered with hexachlorophene (marketed as pHisohex) for three consecutive days before elective operations. At time of surgery, the operative site would once again be scrubbed with pHisohex. All operating room personnel were required to scrub their fingers, hands and arms (up to the area just above the elbow) with brushes and pHisohex for fifteen minutes before participating in any operations. In the delivery room, the vaginal canal was usually cleansed with pHisohex before pelvic examinations were performed. Infants were bathed in pHisohex immediately after birth to remove meconium, amniotic fluid and the vernix caseosa covering them. Hospital personnel were encouraged to wash their hands before touching another patient to prevent cross-contamination and thereby limit nosocomial infections.

An editorial by Husaey in JAMA (1985), was the first to warn of adverse effects in the brain of newborns who developed staphylococcal infections after having been bathed in hexachlorophene. Bhargava et al (1976) reported that the effect on the blood coagulation process after dermal application of hexachlorophene was a reduction in coagulation time, an increase in the number of platelets and an enhancement of the ESR (esinophil sedimentation rate).

Steinbeck (1977), who studied the local and systemic effects of commonly used cutaneous agents on mice and rabbits, reported that the mice showed no local toxic changes or tumor formation, and the systemic tumor incidence, i.e. tumors of the liver, lungs, lymphatic system, and other organs was similar to that of control animals. In rabbits, a number of proliferative benign and malignant ear tumors were observed in the positive controls, thereby demonstrating the efficacy of this model. Local toxic changes were seen in the benzalkonium and
hexachlorophene treated animals, but no skin tumors. Four animals had uterine tumors. In addition, one lung and one kidney tumor unrelated to the method of treatment were seen.

An F.D.A. bulletin (1978) warned of drug induced abnormalities when hexachlorophene was used during pregnancy.

A study by Siddicui et al. (1978) reports that an emulsion containing 0.25% hexachlorophene, 9.5% turpinal, 1.5% oil of turpentine, 13% ethanol, 6% castor oil distillate and 6% sodium salt, when given orally or instilled into conjunctival sacs of albino mice, produced lethal and insignificant toxic manifestations respectively, but a dose equivalent to 50 mg/kg given subcutaneously was found to produce a subacute lethal effect in guinea pigs.

Fischer (1978) reported drug induced abnormalities in newborns exposed to hexachlorophene.

Brandt et al. (1970) examined transplacental passage and embryonic fetal accumulation in mice.

An experiment conducted by Maxwell and Le Quesne (1979) reported that in rats exposed to hexachlorophene for 3 weeks, maximum motor nerve conduction velocity in sciatic nerves was reduced by 7.5%. Histological examination showed intramyelin edema affecting some fibers and axonal degeneration of other fibers. In addition to intramyelin edema and axonal degeneration, segmental demyelination was present in animals who had been intoxicated with hexachlorophene for more than three months. However, there was no correlation between the degree of edema and reduction of conduction velocity.

A letter published in Lancet, 1982, described hexachlorophene poisoning. Another letter by Martin-Bouyer and Stolley published the following week in Lancet described the toxicity of hexachlorophene.

Myers et al (1982) adapted a non-invasive method for measurement of nerve blood flow to test the hypothesis that increased endoneural fluid pressure causes a reduction in nerve blood flow in the vasa nervosum. Their study supports the results that increased endoneural fluid pressure exacerbates the neuropathy by diminishing local blood flow.

Winchell et al (1982) in studying toxic effects of hexachlorophene reported myelin-associated glycoprotein was localized immunocytochemically in periaxonal regions of oligodendraglia during hexachlorophene intoxication.

Using a technique for microgravemetric analysis of nerve edema, Castello, Powell and Myers (1982) demonstrated
increased water content in hexachlorophene neuropathy since there was a marked difference between hexachlorophene treated and control nerves. The water content of hexachlorophene intoxicated nerves was approximately 10% greater than control nerves.

Schwetz (1985) reported adverse effects of environmental agents including hexachlorophene on the central nervous system caused by prenatal exposure.

Rapoport, Menshikova and Bobkova (1985) reported an embryo toxicity associated with hexachlorophene after experimenting with dose induced pathology in guinea pigs.

Using Falck-Hillarp fluorescence histochemistry, Henschenl and Olsen (1983) reported possible toxic effects of hexachlorophene or sympathetic adrenergic nerves. The experiment demonstrated a new aspect of hexachlorophene-neurotoxicity degeneration of peripheral adrenergic nerve terminals and suggested that neurotoxic action on this unmyelinated fiber system should be looked for also in the central nervous system.

Brandt, et al (1983) when studying the placental transfer of hexachlorophene in the Marmoset Monkey found the highest concentration in the liver and intestinal contents of the late fetus and newborn monkey.

Bouin, Buentzet, Pradal (1983) in a study of resorption of drugs through the vaginal wall concluded that hexachlorophene is rapidly and largely absorbed through vaginal epithelium.

Strickland et al (1983) reported that hexachlorophene from vaginal lubricants is variably absorbed from the vaginal mucosa and appreciable amounts can be detected in maternal and cord serum. Because of the potential for neonatal hexachlorophene toxicity, they recommended the use of alternative lubricants for pelvic examinations during labor.

In a comparative study of chemically induced fetal death of mice, Dymin, et al (1984) reported the embryotoxic, gonadotoxic (oligosperma) and mutagenic effects of hexachlorophene.

While studying the effects of reported hexachlorophene treatments on the mouse brain, Prosad et al (1984) concluded the catalytic efficiency of the mouse brain was significantly decreased during repeated hexachlorophene treatment. The fall in the activity potential of ACLE may account for the interference of hexachlorophene which may contribute to its neurotoxicity.
After observing 5 infants with transcutaneous intoxication resulting from hexachlorophene contaminated talcum powder, Larregue et al (1984) described the dermatitis as characterized by its red pants shape, occurring suddenly, its papyraceous aspect, and its association with severe encephalopathy. The neurologic signs with edematous degeneration of myelin characteristic of hexachlorophene toxicity, start with epileptic fits and progress rapidly to coma. The prognosis is serious leading either to death or to paraplegia.

A recently published article by De Caprio et al (1987) examined the in vitro "dioxin-like activity of the environmental contaminant 1,2,4,5,7,8 hexachloro (9H)xanthene. After a number of sites in Missouri had been contaminated with polychlorinated dibenzodioxins and dibenzofurans from improper application of waste oil for dust control, 1,2,4,5,7,8-hexachloro(9H) xanthene, a byproduct of hexachlorophene manufacture was also detected. In view of the potential importance of this class of environmental contaminants, studies were then conducted to examine the acute oil toxicity in guinea pigs of in-vitro "dioxin-like" activity of 1,2,4,5,7,8 HCX. No compound or dose related mortality, body weight loss, or organ weight changes were noted at any dose level. Results using an in vitro bioassay for "dioxin-like" activity confirmed preliminary data suggesting 1,2,4,5,7,8- HCX, is about 10(6) times less potent than 2,3,7,8, tetrachlorodibenzo-p-dioxin (2,3,7,8, TCDD). These findings indicate that 1,2,4,5,7,8 HCX may represent a relatively low environmental hazard compared to 2,3,7,8 TCDD.


Brandt, I; Dencker, L; Larson, Y., Transplacental passage and embryonic-fetal accumulation of hexachlorophene in mice, Toxicol Appl. Pharmacol; 1979, June 30; 49(2):393-401.


Hanig, J.P., Yoder, P.D., Krops, S., Protection with butylated hydroxytoluene (BHY+T) and other compounds against intoxication and mortality caused by hexachlorophene; Food Chem Toxicol; 1984 Mar 22(3):185-9

Henschen, A; Olson,L; Hexachlorophene induced degeneration of adrenergic nerves; a\application of quantitative image analysis to Falch-Hillarp fluorescence histochemistry; Acta Neuropathol (1983)59(2):109-14.
Hexachlorophene-interim caution regarding use in pregnancy. 


Larreque, M., Laidet, B., Ramdene, P., Dyeridi A; Caustic diaper dermatitis and encephalitis secondary to the application of talcum contaminated with hexachlorophene; Ann Dermatol Venereal 1984; 111(9):789-97.


Maxwell, I.C., Le Quesne, P.M., Conduction velocity in hexachlorophene neuropathy: correlation between electrophysiological and histological findings; J. Neurol Sci; 1979 Sep 43(1) 95-110.


Prasad, G.V., Rayendra, W., India K; Catalytic potential of field mouse Mus blduga brain acetylcholinesterase during repeated hexachlorophene treatment, Toxicol Lett; 1984; Nov. 23(2):177-82.

Rapoport, K.A.; Menshikova, T.A., Bobkova, E.A., Experimental data on the study of the embryotoxic acton of hexachlorophene, a component of antimicrobial textiles and household chemicals; Gig. Sanit; 1982 Oct; (10)26-9.


Strickland, D.M.; Leonard R.G.; Staochonskey, S.; Benoit T; Wilson, R.T. Vaginal absorption of hexachlorophene