Teratogenic effects of propineb on rat skin

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Summary

The dithiocarbamates are known to cause dermatitis, conjunctivitis, rhinitis, pharyngitis and bronchitis in humans. The experimental group received Propineb (obtained from Bayer) concentrations of 400 ppm in distilled water five days a week (treatment time three weeks) administered orally by gasric pit. Acute oral LD50 for male rats has been found to be 8,500 mg/kg (Worthing, 1983). The control group (n=10) received only distilled water. At ultrasonographical examination, there were no resorbed fetuses or stillborns during or after propineb administration. It can be clearly seen that the body weights of the experimental group of litters are lower than those of the control group ($p<0.001$). However, the mean length of the experimental litters was identical to the control group of litters ($p>0.05$). Under microscopical examination, increased keratinization and hyperplasia were observed in the epidermal cells.

Key words: Propineb; Rat; Skin.

Introduction

Maneb, zineb, ziram, mancozeb and propineb (zinc propylene bisdithiocarbomates) are a group of organometallic dithiocarbomate fungicides. The dithiocarbamates are considered chemicals of low toxicity. They are known to cause dermatitis, conjunctivitis, rhinitis, pharyngitis, and bronchitis in humans. Central nervous system effects in humans have not been found, but some cases have been reported in experimental animals [1]. Few studies have been carried out on the toxicity of dithiocarbomates containing heavy metals. Mancozeb (Mn and Zn-containing dithiocarbomate) and maneb (Mn-containing dithiocarbomate), two commonly used fungicides, have been shown to induce tumours in mouse skin and rats [2]. Not many studies have been carried out on the organometallic fungicide action or on the fate of fungicides in target organisms. However, many studies have been reported regarding the effects of heavy metals in a variety of organisms. Exposure to most metals results in an accumulation of metals in certain organ tissues of the exposed organisms. It is also known that metals may cause damage to the organs where they accumulate [3]. Hasegawa *et al.* (1993) [4] showed that propineb (Zn dithiocarbomate) causes cancer in the thyroid, kidney and urinary bladder of rats. Zn is known to be essential for prenatal growth and differentiation, and its deficiency causes fetal growth retardation [5]. Mancozeb, a polymeric complex of ethylene bis (dithiocarbamate) manganese with zinc salt, is a protective fungicide. Shukla *et al.* [6] observed complete carcinogenic activity of mancozeb following topical application on dorsal mouse skin.

The purpose of the present study was to histologically assess the teratogenic effects of organometallic fungicide (propineb) during pregnancy on neonatal rat skin.

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Material and Method

Ten female Wistar-albino rats (200-220 gr) were caged and fed standard pellet food during the study. The rats were obtained from the Department of Medical Science Application and Research Centre of Dicle University. The female rats were confined in a special cage over 48 hours for copulation with adult males. After confirming pregnancy with the vaginal smear method, the primipar rats were separated into two groups (total n=8); a control group (n=4) and an experimental group (n=4). The litters in the control (n=10) and experimental group (n=10) were taken. The Experimental group received propineb (obtained from Bayer) concentrations of 400 ppm in distilled water five days a week (treatment time three weeks), administered orally by the gasric pit. Acute oral LD50 for male rats has been found to be 8,500 mg/kg (Worthing, 1983). The control group (n=10) received only distilled water. All experimental gravids were examined daily by a radiologist using ultrasonography (USG). A real time USG (Toshiba SSA-270A) and 7.5 MHz linear transducer was used to detect cardiac activation and to count the number of fetuses. The gravid rats gave birth during the 21st and 22nd days of gestation. Immediately after, all litters were weighed and their lengths were measured. The litters were then anesthetised and several biopsies were taken and fixed in a solution of 10% formaldehyde. The tissues were embedded in paraffin wax, sectioned and stained with hematoxylin-eosin (H&E). Histological assessments were performed using a light microscope.

Results - Discussion

At ultrasonographical examination there were no resorbed fetuses or stillborns during or after propineb administration. It can clearly be seen that the body weights of the experimental group of litters were lower than those of the control group ($p<0.001$) (Table 1). Accordingly, the mean weight of the experimental litters was found to be lower than the control group, however the mean length of the experimental litters was identical to the control group of litters ($p>0.05$), (Table 2).

Table 1. — *Total body weights (g) of the control and experimental groups.*

	X	SD
Experiment (n=10)	5.72	0.04
Control (n=10)	6.09	0.03

Table 2. — *Mean length (cm) of the litters in the control and experimental groups.*

	X	SD
Experiment (n=10)	4.33	0.24
Control (n=10)	4.33	0.22

Vachkova-Petrova *et al.* [7] also found that subchronic exposure to propineb resulted in an interruption of weight gain in wistar rats of both sexes. Propineb was found to cause diarrhea in pregnant female rats which is a well-known clinical picture for acute Zn overload and may well be the reason for the weight loss in the female rats [8]. Although it has been reported that in 2-year feeding trials no ill-effects were found in rats receiving a 50 mg/kg diet [9], the pregnant rats administered 400 ppm propineb for about two weeks had some macroscopic and microscopic effects. Ptosis was observed at the end of pregnancy (Figure 1) following exposure to 400 ppm propineb. Another interesting macroscopic observation at this concentration was that the fungicide caused a rare paralysis at the extremities of the pregnant females, and they rarely got though pregnancy. However, no such effects were observed with their newborn litters. In

Figure 1. — Ptosis appearance at the end of pregnancy (arrow).

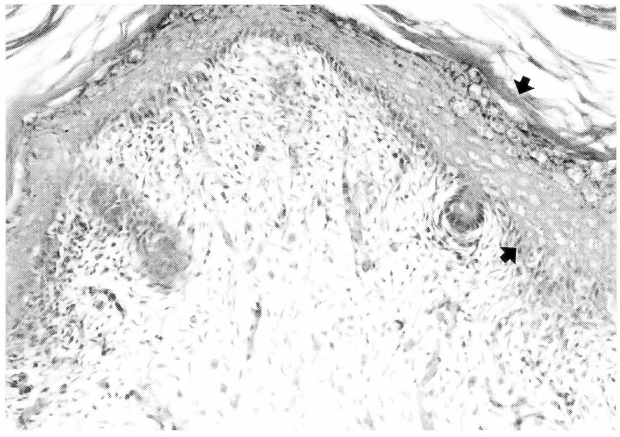

Figure 2. — Increased keratinization and hyperplasia in the epidermal cells (arrow). (H&E, original magnification x 41).

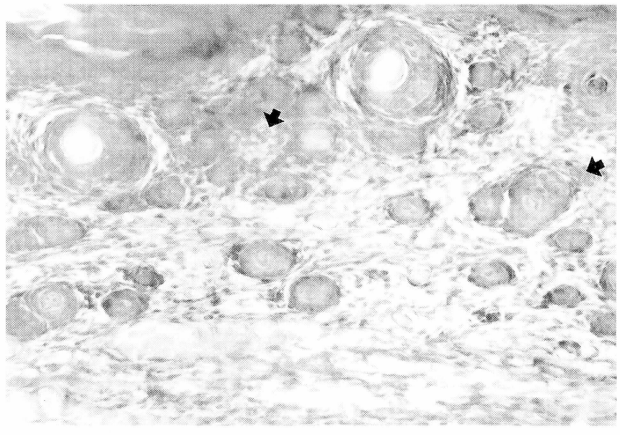

Figure 3. — Chronic inflammatory cell infiltrate in the dermal papillae and around sebaceous glands (arrow). (H&E, original magnification x 41).

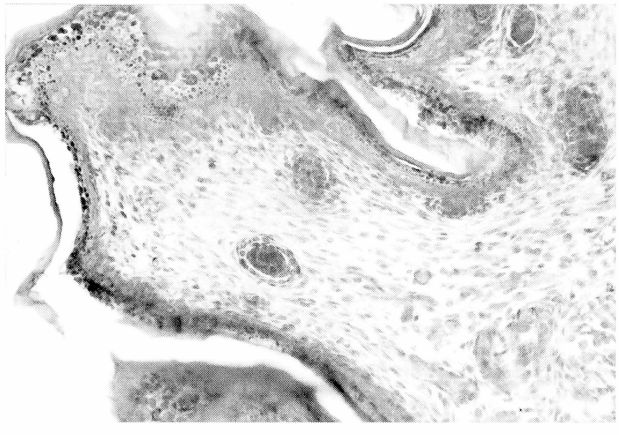

Figure 4. — Normal appearance of the epidermis and dermis. (H&E, original magnification x 41).

animal studies, Propineb has been found to cause squamous cell papillomas and keratoacanthomas on the skin [6]. It has also been known to cause contact dermatitis and eczema in farmers and housewives [1, 10]. Under microscopical examination, increased keratinization and hyperplasia were observed in the epidermal cells (Figure 2). Increased fibrosis and chronic inflammatory cell infiltrates were prominent in the dermal papillae and around the hair follicles (Figure 3). Congestive vessels together with edema and extravasated erythrocytes were noticed in the mid dermis and around the hair follicles (Figure 3). Normal arrangement of the basal layer cells and the dermis were observed in the control group of litters (Figure 4). In a case report, leucocytoclastic vasculitis in association with the use of a propineb patch was diagnosed after a skin biopsy [6]. Although we could not observe any obvious vasculitic damage in our study, there were overall extravasated erythrocytes and considerable teratogenic effects of propineb were observed histologically on newborn rat skin.

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