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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: January 22, 1980

SUBJECT: EPA No.#40510-E; Paranitrophenol for use as fungistat in military shoe leather. Addendum to review of Jan. 15, 1980 by Dr. R. Gessert CASWELL#603

FROM: William S. Woodrow, Ph.D WSW
Toxicology Branch (TS-769)

TO: M. Adrian Gross, Chief William S Butler for M Adrian Gross
Toxicology Branch (TS-769)

Action: Dr. Gessert's review of January 15, 1980, recommends toxicological approval of paranitrophenol incorporated into military footwear leather at 0.7% w/w for use as a fungicide; based on the following toxicity data:

1) Acute oral toxicity, rats.
LD_{50}, male = 191 mg/kg
female = 170 mg/kg
Tox. Cat.: II

2) Acute dermal toxicity, rabbits.
LD_{50} dried crystals = > 10 g/kg
in propylene glycol = 3.69 g/kg
Tox. Cat.: III

3) Primary eye irritation, rabbits.

Severe corneal injury persisting through 7 days.
Tox. Cat.: I

4) Intra dermal guinea pig sensitization. Negative

5) Primary skin irritation, rabbits. Draize score = 1.6 (mild irritant)

6) Teratology, rats. Negative.

8) Mutagenicity - Ames/Salmonella/microsome and yeast tests. Not mutagenic.

9) Army skin patch and wear tests. Skin patch testing showed treated leather applied directly to skin caused some irritation, whereas wear tests were negative, possibly because socks were worn.

Recommendation (by Woodrow)

Acting in the capacity of Section Head at the time Dr. Gessert's review was completed, I do not agree with his recommendation that the subject use of paranitrophenol in military footwear is toxicologically supported. My concerns include the following:

1. We do not have results of long-term animal studies to base predictions of long-term human exposure.

2. Current toxicological approval would result in exposure to approximately 2.5 million men and women in the military service. Following such approval, one can foresee the entire American public and perhaps world wide use of paranitrophenol in footwear within a short time.

3. The registrant states that the following studies are now in progress:

   a) A dermal penetration study using ^{14}C - labeled PNP.

   b) Carcinogenicity studies are being conducted under the arespices of the National Cancer Institute.

4. Based on the toxicity data evaluated to date, the use of paranitrophenol in military footwear would not appear to present visible human hazard; however, a toxicity profile is not complete - no chronic data are available.

Information on paranitrophenol dermal penetration, metabolism, and ultimate fate of the parent compound and its metabolites should be made available to Tox. Branch. According to Robinson, et al, 1951*, ortho, meta, and paranitrophenols are eliminated by rabbits in the urine mainly in the conjugated form as nitrophenyl glucoronides and as ethereal sulfates. These authors state that 14% of the nitro group of paranitrophenol is reduced.

Such reduction could possibly result in nitrosamine formation mediated through a paranitrophenol intermediate as a result of the reduction process. If all of the parent PNP is excreted as the above authors suggest, probably no human hazard exists; until such evidence is confirmed, a potential for formation of hazardous intermediate compounds may exist.

*Robinson, D.; Smith, J.N.; and Williams, R.T.: Biochem. J., 50, 221, 1951.

I suggest that more or less permanent toxicological approval for EPA 40510-E use of PNP be deferred until results of the dermal penetration and chronic studies are available, and further suggest that some type of temporary, emergency type of toxicological approval be considered until Toxicology Branch evaluates the results of both of these studies.

At present, a NOEL for dermal irritation is not available. It is my opinion that in addition to the dermal penetration and chronic rat study now being conducted with PNP, a subchronic dermal irritation study in rats to determine a NOEL should be performed to properly predict human hazard.