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Report 6-46

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TOXICITY OF DIISOCYANATES

Attached is a summary of preliminary work done in this Laboratory on the two diisocyanates sent us recently. While this report gives comparative data on acute toxicity to laboratory animals, it does not necessarily follow that the early effects which you might detect in workers would show the same difference in trend between the two compounds.

HASKELL LABORATORY OF
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Summary of Acute Toxicity Studies on Two Isocyanates

Two compounds were received from for test. These were:

I Hexamethylene-diisocyanate

II Diisocyano-diphenylmethane

PROCEDURE:

Each of six rats received a single oral dose of each compound. With Diisocyano-diphenylmethane the maximum feasible oral dose killed no rats. After waiting twelve days for the appearance of delayed effects, each of six rats received daily 2 cc. of 1:1 II in corn oil by mouth for five successive days.

RESULTS:

A. Hexamethylene-diisocyanate

Rat	Single Oral Dose (gm/kg)	Results
A	0.28	Sacrificed after 10 days
B	0.42	Sacrificed after 10 days
C	0.62	Sacrificed after 10 days
D	0.94	Died within 24 hours
E	1.4	Died within 24 hours
F	2.1	Died within 24 hours

Estimated minimum lethal dose = 0.94 mg/kg

Rats D, E, and F on autopsy showed congestion of the lungs and spleen, and evidence of gastric irritation reflected in edema and cyanosis of the mucosa, and some necrosis of superficial cells of the mucosa.

Rats A, B, and C were observed for 10 days after the single dose of IPD-312. All showed a slight weight loss (av.= 7%) over the first five days of observation, but had regained their original weight by the end of the second five days. After 10 days Rats A, B, and C were sacrificed. On autopsy, all showed congestion of the spleen and evidence of gastric irritation. Rats B and C showed in addition slight peribronchial edema of doubtful significance.

B. Diisocyano-diphenylmethane (Pure compound contains no ortho dichlorobenzene

1) Single dose

Rat	Single Oral Dose (gm/kg)	Results
A	0.62	No apparent ill effect in 12 days
B	0.94	" " " " " " "
C	1.4	" " " " " " "
D	2.1	" " " " " " "
E	3.3	" " " " " " "
F	4.7	" " " " " " "

2) Repeated doses at end of original 12 day observation period.

Rats A, B, C, D, and F received daily oral doses of 2 ml. of 1:1 I for five successive days. Rats weighed between 200 and 230 gms. so that dose was equivalent to 4.3 to 5.0 gm/kg/day. Three days after the final dose, no apparent ill effects had appeared so animals were sacrificed. On autopsy, Rats C, D, and F showed no pathology; Rats A and B showed slight enlargement of the spleen, and Rat E showed a tapeworm cyst of the liver which had no relation to the compound tested.

DISCUSSION:

On the basis of the above experiments, hexamethylene-diisocyanate appears to be a toxic and irritant compound whose minimum lethal oral dose for rats is of the order of 1 gm/kg. This compares with a minimum lethal oral dose of 0.6 gm/kg for white mice, reported by Imperial Chemical Industries. I.C.I. also found I to be extremely irritant to the eyes of rabbits, and extremely irritant to the skin of mice and rats. Sufficient I can be absorbed through the skin of mice and rats to cause death. I.C.I. also reports that in man, I can produce skin and eye irritation, and conclude that the compound requires careful handling.

Diisocyano-diphenylmethane appears from our experiments to be far less toxic than the aliphatic compound. Imperial Chemical Industries also studied this compound and found that white mice tolerated a dose of 1.0 gm/kg without symptoms. The compound was not more irritating to rabbits' eyes than the solvent in which it was dissolved. No irritant effects on human skin were observed by I.C.I.

CONCLUSIONS:

Hexamethylene-diisocyanate is a dangerous compound from the point of view of both contact and ingestion hazard. Diisocyano-diphenylmethane is relatively nonhazardous so far as contact and ingestion are concerned, on the basis of our limited experiments and those reported by Imperial Chemical Industries.

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