MRI# 316060

8ehq_1208-17360A
DCN: 88090000084

DuPont Haskell Global Centers
for Health and Environmental Sciences
1090 Elkton Road, P.O. Box 50
Newark, DE 19714-0050

8EHQ-09-17360

December 30, 2008

Via Federal Express

Document Processing Center (Mail Code 7407M)
Room 6428
Attention: 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
1201 Constitution Ave., NW
Washington, DC 20004

RECEIVED
OPPT CBIC
09 Jan 2.

88090000084

Dear 8(e) Coordinator:

Acetylsalicylic Acid
CAS # 50-78-2

This letter is to inform you of the results of a pre-1977 (1967) concentration x time acute inhalation toxicity study in guinea pigs, which we recently became aware of with the above referenced test substance. This study was conducted under a government contract, and DuPont does not manufacture, import or process the test substance.

Acetylsalicylic acid was prepared as an aerosol by use of a paint spray jet. Guinea pigs were exposed for one or ten minutes to various concentrations in a standard 16-liter exposure chamber. Observations of reactive signs were made over a 2-hour period. At 24 hours after exposure, weight loss was measured, eyes examined, and any reactive signs noted. At the lowest dosage level, the lungs were removed at 24 hours and their volumes measured.

The results showed general signs of irritation at the higher level including face-pawing, lacrimation, salivation, and coughing. At lower levels, salivation and lacrimation were an indication of irritation. The general indications of dyspnea were related to increased lung volume. Measurement of lung volumes in relation to body weight for the group of animals exposed to 2000 μg/L x min (CT) reveals relative volumes of 1.5, 2.5, 2.4, and 2.1 ml/100 g (relative to body weight). The normal relative volume is 0.7 ml/100 g. Thus, lung enlargement was a result of this treatment. Only one death in the group of four was recorded in these experiments for an exposure of 9000 μg/L x min (CT). At a higher level 20,000 μg/L x min (CT), no deaths in a group of four were observed. Also, the weight loss over the first 24-hour post-exposure was minor. Moderate opacity of the cornea was seen in some of these animals and is attributed to the direct local corrosive effect.

At the highest level, tremors, loss of righting reflex, uncoordinated movement, and prostration were seen and interpreted as signs of central nervous system activity of the chemical and an indication that the chemical entered the brain.

This information is submitted in accordance with current guidance issued by EPA indicating EPA's interpretation of Section 8(e) of the Toxic Substances Control Act or, where it is not clear that reporting

Contains No CBI

CONTAINS NO CBI

criteria have been met, it is submitted as a precautionary measure and because it is information in which EPA may have an interest.

A copy of the report is attached.

Sincerely,

A. Michael Kaplan

A. Michael Kaplan, Ph.D.
Director - Regulatory Affairs

AMK/BPS: clp
(302) 366-5260

Attachment: 5 pages

MR# 316060

Covering Letter dated 6-2-67

[redacted]

TO BE OPENED BY ADDRESSEE ONLY

RECEIVED
DDC/TSIC
08 DEC 33 AM 8:21

INCREASED EFFECTIVENESS BY AEROSOL ADMINISTRATION OF ACETYLSALICYLIC ACID IN CONTRAST TO ORAL TREATMENT

SUMMARY

Pronounced CNS signs were seen in guinea pigs treated with acetylsalicylic acid as an aerosol at levels which, on the basis of known oral toxicity data should have been well tolerated. These signs included loss of righting reflex, tremors, uncoordinated movements, and prostration. Incidences of corneal opacity were found in unprotected eyes. Signs of dyspnea were associated with increased relative lung volume. Ancillary work showed a linear relationship of the yield of respirable aerosol to solvent composition.

These data are interpreted in terms of realization of a shorter pathway to the brain. Conventional entrance of chemicals to the body is mediated by the gastric or peripheral venous system and then through the portal system before access to the brain is possible. However, lung absorption presents a portion of the chemical directly to the brain after a single passage through the heart.

INTRODUCTION

The introduction of chemicals by inhalation is unique in that such chemicals are presented directly to the brain without chemical alteration in the liver or by the gastric system. The flow of blood from the lungs is to the heart and then a large portion is sent to the brain. Inhalation of potential central nervous system (CNS) active agents may be studied conveniently as a simple blood-brain barrier problem. Because of its known ease of hydrolysis in the body, acetylsalicylic acid was chosen to explore this hypothesis. Preliminary efforts indicate that the CNS effect observed is greater than might be expected by more convential routes of administration.

METHOD

Acetylsalicylic acid was prepared as an aerosol by use of a paint spray jet. Guinea pigs were exposed for one or ten minutes to various concentrations in a standard 16-liter exposure chamber. Observations of reactive signs were made over a 2-hour period. At 24 hours after exposure, weight loss was measured, eyes examined, and any reactive signs also noted. At the lowest dosage level, the lungs were removed at 24 hours and their volumes measured.

ADDRESSEE ONLY

METHOD (Continued)

The generation of aerosol from methylene chloride alcohol mixtures was investigated briefly to help explain the observed deposits seen on the inside of the exposure chamber.

RESULTS AND DISCUSSION

The preliminary results are tabulated (Table I) and show general signs of irritation at the higher level including face-pawing, lacrimation, salivation, and coughing. At lower levels, salivation and lacrimation remain as an indication of irritation. The general indications of dyspnea are related to increased lung volume. Measurement of lung volumes in relation to body weight for the group of animals exposed to 2000 μg/L x min (CT) reveals relative volumes of 1.5, 2.5, 2.4, and 2.1 ml/100 g (Relative to Body Weight). The normal relative volume is 0.7 ml/100 g. Thus, lung enlargement is a result of this treatment. Only one death in group of four was recorded in these experiments for an exposure of 9000 μg/L x min (CT). At a higher level 20,000 μg/L x min (CT), no death in a group of four was found. Also, the weight loss over the first 24-hour post-exposure was minor. Moderate opacity of the cornea was seen in some of these animals and is attributed to the direct local corrosive effect.

At the highest level, tremors, loss of righting reflex, uncoordinated movement, and prostration were seen and interpreted as signs of central nervous system activity of the chemical and an indication that the chemical entered the brain.

On the basis of a minute volume of 400 ml/min for guinea pigs of this size (data of M. McLaughlin) and a dosage of 20,000 μg/L x min (CT), these 500 g animals received 8 mg of acetylsalicylic acid or 16 mg/kg (body weight). This dosage level necessary for pronounced CNS effects is distinctly lower than the approximate 1700 mg/kg oral toxicity for rats and mice (Merck Index and C. A. 62, 9628). In general, the toxic effects of high doses of salicylates are seen neurologically as stimulation followed by depression along with confusion, dizziness, tinnitus, high-tone deafness, delirium, psychosis, stupor, and coma (cf. Goodman and Gilman, 3rd Edition, p. 315). Thus, the comparison of CNS signs seen in the aerosol treated guinea pigs with low dosages, with reported toxicity signs, confirms the observation that administering of chemicals to the brain is expedited by use of respirable aerosols.

By variation of composition of a methylene chloride/alcohol system and keeping a 5% total concentration of acetylsalicylic acid, various efficiencies of production of respirable aerosols were realized. Table II shows these results. The linearity of aerosol concentration as a function of composition is shown in Figure I. A ninefold increase in aerosol yield was achieved when the solvent was changed from ethanol to methylene chloride. This is contrasted with the solubility of acetylsalcylic acid which is about 5% in methylene chloride and about 20% in alcohol at room temperature.

TABLE I

RESPONSE OF GUINEA PIGS TO ACETYLSALICYLIC ACID AEROSOL

SCORE* VS. DOSAGE

Dosage CT (μg/L/min)	Dyspnea	Face Pawing	Lacrimation	Salivation	Gasping (Coughing)	Ptosis	Tremors (Shaking)	Loss of Righting	Hind Leg Weakness Uncoordinated	Prostration	Opaque Cornea (24 hrs.)	Weight Loss - % (24 hrs.)	No.	Ref. 5889-
20,000	28	4	12	4	4	24	20	20	12	4	(+)	-	4	129
9,000	28	-	-	-	4	-	-	+	16	-	+	2.5	4	153
6,300	28	-	-	-	+	8	-	-	-	-	+	3.5	4	154
5,800	28	6	-	-	-	6	+	-	-	-	+	1.5	4	154
2,000	16	-	8	6	-	-	-	-	-	-	(?)	4.5	2	129
2,000	16	-	9	1	-	-	-	-	-	-	(?)	0	2	129

* Score is product of maximum observed reactive sign on a scale of 1 to 4 multiplied by the duration in time coded as follows:

Time Block Min.	0-3	5	10	20	30	60	120
Code	1	2	3	4	5	6	7

TABLE II

PARTICLE SIZE AND AEROSOL YIELD WITH VARIATION IN SOLVENT COMPOSITION

Composition of Solvent (% v/v)		Aerosol Concentration	Size (MMD)		Ref.
Ethanol	Methylene Chloride	mg/L	Micron	σ	5889-
100	0	0.420	3.8	1.65	155
100	0	0.580	1.5	2.33	154
100	0	0.630	1.4	2.43	154
90	10	1.44	1.8	3.10	155
75	25	1.45	2.2	2.72	155
50	50	1.55	3.3	2.28	155
50	50*	2.06	2.1	3.05	126
25	75	2.55	3.0	2.66	155
0	100	2.86	3.9	3.25	155

* Concentration of solute-acetylsalicylic acid 3%. All other runs concentration 5%.

Nominal Concentration Calculation

At a liquid input of 10 ml/min of a 5% (w/v) solution and a gross air flow of 36 liter/min, the nominal concentration of solid in air is as follows:

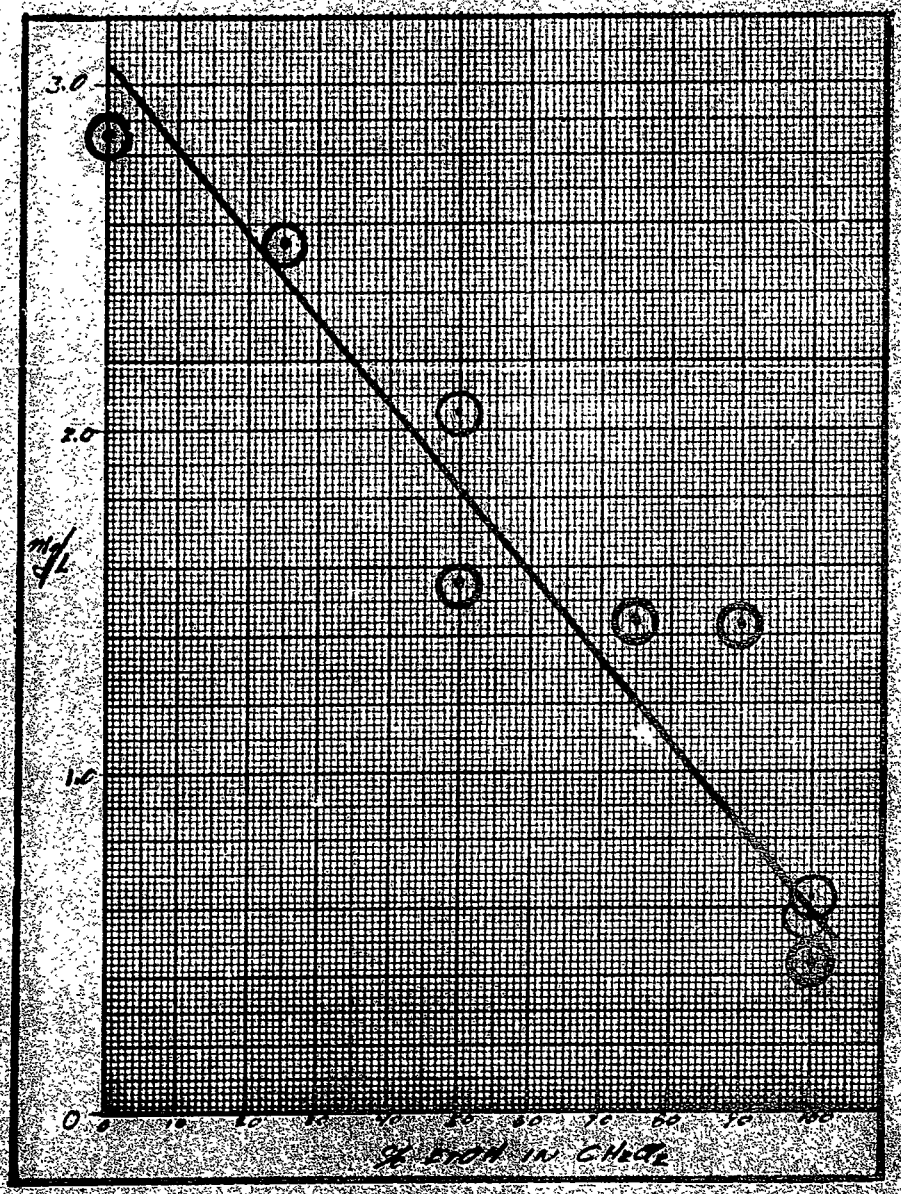
$$\frac{(0.05\ g/ml)\ (10\ ml/min)\ (1000\ mg/g)}{36\ liter/min} = 14\ mg/L$$

On this basis, the yield of respirable aerosol varied from 2.9% (low value for ethanol) to 20.4% (high value for pure methylene chloride). Furthermore, the higher conversion to aerosol correlates with lower solubility since a 5% concentration of acetylsalicylic acid in methylene chloride is near saturation at room temperature whereas a 20% solution in ethanol is possible.

FIGURE I

AEROSOL YIELD VS. SOLVENT COMPOSITION

FROM ASPIRIN
(MMD < 5 μ)



SBBP-155