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The Toxicological Properties of Hydrocarbon Solvents

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Hydrocarbon solvents are widely used in industry, either aromatic or saturated compounds or both. A study is presented testing ten representative compounds for toxicity, giving relative grade to each.

INTRODUCTION

The annual consumption of hydrocarbon solvents in the United States is estimated at 1.3 billion gallons.[1] A major portion of this is used in paints and other surface coatings and in the dry cleaning industry. Large quantities are also used in the extraction of soybean oil, cottonseed oil and fish oil, in the manufacture of printing inks and rubber cement, as lighter fluids, and as solvents for pesticides.

A few of these solvents, e.g. benzene (benzol), toluene (toluol), xylene (xylol) and hexane, are known commercially by their chemical names. Others are commonly described by generic terms such as VM&P naphtha, petroleum ether, rubber solvent, Stoddard Solvent, mineral spirits, deodorized kerosene, and aromatic solvent. In addition, many solvents are supplied under trade names.

Hydrocarbon solvents consist almost entirely of either aromatic or saturated compounds or both. The aromatics are principally derivatives of benzene, although those with a higher boiling point may contain derivatives of naphthalene as well. The saturates include straight chain compounds, e.g., n-hexane, branched chain or "iso" compounds, e.g., 2-methyl pentane or isohexane, and cyclic compounds, e.g., cyclohexane, or hexahydrobenzene. The saturated cyclic hydrocarbons, or naphthenes, occurring in hydrocarbon solvents are largely derivatives of cyclohexane or cyclopentane.

The molecular size of the compounds present in the commonly used hydrocarbon solvents ranges from C-6 to about C-15. The C-6 hydrocarbons predominate in solvents boiling below 180F (82C). C-15 compounds are found in kerosene and solvents boiling in the vicinity of 500F (260C).

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Various solvents differ greatly in complexity of composition. Benzene and toluene are essentially pure compounds, whereas others such as hexane and xylene consist of a small number of isomers. However, the number of possible isomers increases rapidly with increasing molecular weight. Furthermore, most solvents do not have a constant boiling point, but are mixtures possessing a boiling range. The spread between initial and final boiling point is usually less than 50F (10C), but it may be as much as 200F (93C) or more. Gerarde[2] found more than 50 compounds in an aromatic solvent which has a boiling range of about 50F. Products with wider boiling range and containing both saturated and aromatic components could easily contain hundreds of individual hydrocarbons.

The test program reported here was undertaken to develop systematic toxicity data on a reasonable number of well-defined samples representing the types of hydrocarbons found in commercial solvents, since there is a paucity of published information, despite the widespread use of these solvents and the frequency of human exposure. Ten samples were selected – four aromatic and six saturated. These, together with benzene and toluene, cover the boiling range normally found in hydrocarbon solvents. The four aromatic samples were prepared by concentrating the aromatics in commercial products by an adsorption technique. The finished samples contained at least 98% aromatics. Benzene and toluene were not included in the major part of this study since considerable published information[2-4] is available on these compounds. The saturated samples were prepared by treating commercial products with adsorbent for removal of aromatics, and all six final samples contained less than 1% aromatics. All of the samples except S-5 are derived from products obtained from petroleum by processes of physical separation (distillation and solvent extraction). Sample S-5 was derived from a synthetic product made from petroleum gases by the aklylation process.

The ten products used in preparation of the test samples were supplied by Shell Chemical Company, Petrochemicals Division.

METHODS AND MATERIALS

A. *Test Samples:*

The ten samples and their boiling ranges and principal components were as follows:

Sample	*Boiling Range*	*Principal Components*
A-1	281-286F (138-141C)	C-8 aromatics (ortho, meta and para xylene; ethyl benzene)
A-2	362-398F (163-203C)	C-9, C-10 and C-11 aromatics
A-3	364-408F (188-209C)	C-10 and C-11 aromatics
A-4	384-507F (196-264C)	C-11 thru C-14 aromatics
S-1	149-166F (65-75C)	C-6 normal and iso paraffins (hexanes) and naphthenes (cyclo-hexane, methyl-cyclopentane).
S-2	196-220F (91-104C)	C-7normal and iso paraffins (heptanes) and naphthenes (methyl-cyclohexane, dimethyl-cyclopentane)
S-3	313-356F (156-180C)	C-9 and C-10 normal and iso paraffins and naphthenes
S-4	368-395F (187-212C)	C-11 and C-12 normal and iso paraffins and naphthenes
S-5	345-402F (174-216C)	C-12 isoparafi
S-4	368-395F (187-212C)	C-11 and C-12 normal and iso paraffins and naphthenes
S-5	345-402F (174-216C)	C-12 isoparaffins
S-6	384-500F (195-260C)	C-13 thru C-16 normal and iso paraffins and naph..nenes.

Acute oral, vapor inhalation and percutaneous toxicity tests were conducted on all ten samples, together with primary skin and eye irritation tests. Aspiration tests were run on two of the samples (A-4 and S-6), and repeated skin irritation studies were made on seven (benzene, toluene, A-1, A-3, S-1, S-5 and S-6).

All of the tests were conducted on undiluted samples.

B. *Test Animals*

All rats used were Long-Evans males weighing between 150 and 300 gm. Rabbits were albino (New Zealand white) males weighing 2 to 3 kg. In all acute tests, animals were retained a minimum of 14 days after dosing, and mortality values were based on the number of animals which died during this interval. LD_{50} values were determined by the method of Litchfield and Wilcoxon. Estimated values are given where this method could not be applied.

C. *Test Methods*

1. *Acute Oral Administration:* Graded doses up to 25 ml/kg were injected intragastrically, using six rats per dose in most cases.

2. *Vapor Inhalation:* A 250-liter chamber was used for the vapor exposures. Air entering the chamber was bubbled through the sample, heated to 77F (25C) in a water bath in order to obtain an atmosphere as close to saturated as possible. Vapor concentration in the chamber was monitored by means of a Wilkens Aerograph GLC and compared with the vapor concentration obtained from a bottle known to contain vapors saturated at 25C. For graded concentrations less than saturated, the air flow entering the chamber was divided so that only part of it passed through the sample. Rats were exposed for four hours and ten rats were used for each exposure.

3. *Aspiration:* Rats were anesthetized to the point of apnea with ether and made to aspire 0.2 ml of sample, according to the method of Gerarde.[5] All animals were observed closely and posted as soon after death as possible. Lung weights obtained in rats that died and in survivors sacrificed at 24 by exsanguination. Ten rats were used for each of th solvents, and additional groups were used for the negati positive controls. Negative controls were rats that receiv treatment other than anesthetization with ether, and whic sacrificed at 24 hours. Positive controls aspirated kerosene.

4. *Primary Skin Irritation:* Each sample was applied t intact and abraded skin of six shaved rabbits. Application were covered with gauze for 24 hours, and readings fo irritation, according to the method of Draize, were made and 72 hours. A maximum of four samples was applied to rabbit.

5. *Eye Irritation:* Approximately 0.1 ml of sample was p in the conjunctival sac of one eye of each of six rabbits other eye serving as a control. Readings for eye irrita according to the Draize system, were made at 24, 48 an hours.

6. *Percutaneous Administration:* Graded doses of sample t 5.0 ml/kg were introduced under a Saran-wrap sleeve to ea three shaved rabbits. Contact was maintained for four h after which time the covering was removed and the skin w off with damp towels. Animals were observed for sign toxicity, and mortality.

7. *Repeated Skin Irritation:* Two groups of 6 rabbits each used. The animals in the first group were given daily applicat of S-4, A-1, benzene, and toluene for 10 days. The second gr were given daily applications of A-3, S-1, and S-6.

The experiments were arranged so that no two ani received the material on the same area of the back.

Each application consisted of 0.5 ml of sample. No atte was made to remove excess material after exposure. Observat for irritation were made daily and scored according to method of Draize.

RESULTS

1. *Acute Oral Administration*

A-1: The LD_{50} was 10.0 ml/kg with confidence lim of 7.5 to 13.3 ml/kg. Most deaths occurred during first 72 hours after dosing.

A-2: The LD_{50} was 4.5 ml/kg with confidence lim of 3.0 to 6.8 ml/kg. Deaths occurred from the first fifth days.

A-3: The LD_{50} was 13.3 ml/kg with confidence lim of 7.5 to 23.7 ml/kg. Deaths occurred within three da and partial mortality was distributed over a wide ran of doses.

A-4: The LD_{50} was 12.3 ml/kg with confidence lim of 8.1 to 18.7 ml/kg. Deaths occurred on the second fourth days.

S-1: No deaths resulted from doses as high as 25 ml/kg.

S-2: A dose of 25.0 ml/kg, the highest used, resulted the death of one rat out of six, on the fifth day.

S-3: No deaths resulted from doses as high as 25 ml/kg.

S-4: No deaths resulted from doses as high as 25 ml/kg.

S-5: No deaths resulted from doses as high as 25 ml/kg.

S-6: No deaths resulted from doses as high as 25 ml/kg.

2. *Vapor Inhalation:*

A-1: The LD_{50} was 6350 ppm with confidence limits of 4670 to 8640 ppm or approximately 50% to 90% of saturation at 25C. All deaths occurred during exposure. Survivors were comatose, but recovered shortly after removal from the chamber.

A-2: The highest chamber concentration that could be attained was 2450 ppm, or 93% of saturation. There were no deaths at this level.

A-3: The highest chamber concentration which could be attained was 580 ppm or 44% of saturation at 25C. There were no deaths at this level.

A-4: The highest chamber concentration that could be attained was 553 ppm or 84% of saturation. There were no deaths at this level.

S-1: The LD_{50} was 73,680 ppm with confidence limits of 66,310 to 79,940 ppm, or approximately 30 to 40% of saturation at 25C. All deaths occurred during the 4-hour exposures with the exception of one rat in the 81,800 ppm exposure who had convulsions during and after exposure and died on the sixth day. Rats that survived were uncoordinated, prostrate or comatose during exposure, but recovered within a few hours after removal from the chamber.

S-2: The LD_{50} was between 14,000 and 16,000 ppm, or 25 to 30% of saturation at 25C. Fractional mortality was quite variable between 11,000 and 15,000 ppm and survivors at these levels were comatose during exposure; only one rat exhibited convulsions. All deaths occurred during exposure.

S-3: The LD_{50} was between 2000 and 2600 ppm, or 80 to 100% of saturation at 25C. The 100% mortality at 921 ppm was discounted as an anomalous exposure, since both 1000 ppm and 1950 ppm exposures resulted in no deaths. Most of the deaths occurred during the exposure intervals.

S-4: The highest chamber concentration that could be attained was 710 ppm or 54% of saturation at 25C, on the 11th day after exposure, one rat out of ten died, perhaps not as a result of the exposure.

S-5: The highest chamber concentration that could be attained was 592 ppm or 45% of saturation at 25C. There were no deaths at this level.

S-6: The highest chamber concentration that could be attained was 263 ppm or 40% of saturation at 25C. There were no deaths at this level.

3. *Aspiration*

Negative control rats given ether anesthesia and sacrificed at 24 hours had normal lung weights. Of the nine positive control rats that aspirated kerosene, four died within four hours and one died overnight. Lung weights of these were increased three or four times above normal. Lung weights of the survivors at 24 hours were more than twice normal.

Sample A-4: Of the ten rats aspirating sample A-4, five died immediately, and five were sacrificed at 24 hours. All lung weights were elevated 40% to 50% above normal.

Sample S-6: Of the ten rats aspirating sample S-6, three died within five hours, two died overnight, and the remaining five were sacrificed at 24 hours. Lung weights of survivors were increased about 70% above normal, while lung weights of those that died were increased three or four times above normal.

4. *Primary Skin Irritation:*

A-1: The average primary irritation score was 2.21. All six rabbits were affected on both intact and abraded skin, and individual scores ranged from 1 to 4.

A-2: The average primary irritation score was 2.04. Individual scores ranged from 0 to 3 on both intact and abraded skin, but most scores were either 2 or 3.

A-3: The average primary irritation score was 2.17. Scores ranged from 1 to 4, and both intact and abraded skin were affected.

A-4: The average primary irritation score was 2.79. Individual scores ranged from 1 to 4 on both intact and abraded skin, but most scores were 2, 3 or 4.

S-1: The average primary irritation score was 1.92, with all six rabbits showing degrees of irritation ranging from 1 to 3 on both intact and abraded skin.

S-2: The average primary irritation score was 1.13. Individual scores ranged from 0 to 2 on both intact and abraded skin.

S-3: The average primary irritation score was 2.38. Scores ranged from 1 to 3 on both intact and abraded skin, but irritation was more pronounced at 72 than at 24 hours.

S-4: The average primary irritation score was 1.04. Individual scores ranged from 0 to 2 on both intact and abraded skin, with irritation slightly more pronounced at 72 than at 24 hours.

S-5: The average primary irritation score was 1.29. Individual scores ranged from 0 to 3 on both intact and abraded skin.

S-6: The average primary irritation score was 0.75. Individual scores ranged from 0 to 2, but abraded skin was primarily affected.

5. *Eye Irritation:*

A-1: The average eye irritation scores were 5.33 at 24 hours, 6.33 at 48 hours and 4.67 at 72 hours. Irritation was confined to the conjunctiva, but all six rabbits were affected.

A-2: Average eye irritation scores were 4.67 at 24 hours, 6.0 at 48 hours, and 4.33 at 72 hours. Irritation was confined to the conjunctiva, but all rabbits were affected.

A-3: The average eye irritation scores were 4.33 at 24 hours, 2.33 at 48 hours and 4.33 at 72 hours. Irritation was confined to the conjunctiva.

A-4: Average eye irritation scores were 3.33 at 24 hours, 3.67 at 48 hours, and 3.33 at 72 hours. Irritation

TABLE 1. Summary of Results

Test	*Sample*	*Score*	*Classification*
Oral	A-1	10.0(7.5-13.3)	practically non-toxic
LD_{50}	A-2	4.5(3.0-6.8)	slightly toxic
(ml/kg)	A-3	13.3(7.5-23.7)	practically non-toxic
	A-4	12.3(8.1-18.7)	practically non-toxic
	S-1	>25.0*	relatively harmless
	S-2	>25.0*	relatively harmless
	S-3	>25.0*	relatively harmless
	S-4	>25.0*	relatively harmless
	S-5	>25.0*	relatively harmless
	S-6	>25.0*	relatively harmless
Vapor	A-1	6,350(4,670-8,640)	slightly toxic
Exposure	A-2	>2,450†	SVNTART‡
LC_{50} in ppm	A-3	>580†	SVNTART
for 4 hours	A-4	>553†	SVNTART
	S-1	73,680(66,310-79,940)	practically non-toxic
	S-2	14,000-16,000	practically non-toxic
	S-3	2,00-2,600	slightly toxic
	S-4	>710†	SVNTART
	S-5	>792†	SVNTART
	S-6	>263†	SVNTART
Aspiration	A-4	5/10	hazardous
(mortality)	S-6	5/10	hazardous
Primary	A-1	2.21	moderately irritating
Skin	A-2	2.04	moderately irritating
Irritation	A-3	2.17	moderately irritating
	A-4	2.79	moderately irritating
	S-1	1.92	slightly irritating
	S-2	1.13	slightly irritating
	S-3	2.38	moderately irritating
	S-4	1.04	slightly irritating
	S-5	1.29	slightly irritating
	S-6	0.75	minimally irritating
Eye	A-1	6.33	moderately irritating
Irritation	A-2	6.0	moderately irritating
	A-3	4.33	moderately irritating
	A-4	3.67	slightly irritating
	S-1	0.33	minimally irritating
	S-2	1.0	minimally irritating
	S-3	2.0	minimally irritating
	S-4	0	minimally irritating
	S-5	0	minimally irritating
	S-6	0	minimally irritating
4-hour	A-1	approx. 5.0	practically non-toxic
Percutaneous	A-2	approx. 5.0	practically non-toxic
LD_{50} Rangefind	A-3	approx. 5.0	practically non-toxic
(ml/kg)	A-4	approx. 5.0	practically non-toxic
	S-1	>5.0	practically non-toxic§
	S-2	>5.0	practically non-toxic§
	S-3	>5.0	practically non-toxic§
	S-4	approx. 5.0	practically non-toxic
	S-5	>5.0	practically non-toxic§
	S-6	>5.0	practically non-toxic§
Repeated	Benzene	3.6	
Skin	Toluene	3.5	
Irritation	A-F	3.3	

* Doses above this amount not practical for testing.
† Maximum concentration obtainable at 25C.
‡ Saturated vapors not toxic at room temperature.
§ Lowest toxicity classification may be "relatively harmless."

was confined to the conjunctiva and all rabbits were affected.

S-1: One rabbit out of six had a score of 1 for redness at 24 hours. All other readings were negative.

S-2: Average eye irritation scores were 1.0 at 24 hours, 0.67 at 48 hours and 1.0 at 72 hours. Only the conjunctiva was affected and only half the animals showed irritation.

S-3: Average eye irritation scores were 2.0 at 24 hours, 2.0 at 48 hours, and 1.67 at 72 hours. Irritation was confined to the conjunctiva, and not all rabbits were affected.

S-4: All readings at 24, 48 and 72 hours were negative.

S-5: All readings at 24, 48 and 72 hours were negative.

S-6: All readings at 24, 48 and 72 hours were negative.

6. *Percutaneous Administration*

A-1: The highest dose of 5.0 ml/kg resulted in the death of one rabbit out of three on the fifth day after exposure. Survivors evidenced discomfort and prostration during exposure. No deaths occurred at a dose of 2.0 ml/kg.

A-2: One of three rabbits died on the fourth day after a dose of 5.0 ml/kg. Discomfort was evidenced at this level. No deaths resulted from a dose of 2.0 ml/kg.

A-3: One out of three rabbits died after a dose of 5.0 ml/kg. The death occurred on the second day after exposure. At this level, animals exhibited incoordination during and immediately after exposure. No deaths resulted from a dose of 2.0 ml/kg.

A-4: One of three rabbits died on the second day after a dose of 5.0 ml/kg. No deaths occurred after a dose of 2.0 ml/kg. All animals evidenced discomfort.

S-1: No deaths occurred at the highest dose of 5.0 ml/kg, but rabbits evidenced discomfort and were incoordinated at the end of the four-hour exposure.

S-2: No deaths resulted from a dose of 5.0 ml/kg, but discomfort was evidenced during exposure.

S-3: At a dose of 5.0 ml/kg, all animals survived, but evidenced discomfort during exposure.

S-4: At a dose of 5.0 ml/kg, one rabbit out of three died on the second day after exposure, and a second rabbit died on the 16th day. The latter was not included in the 14-day mortality data. No deaths occurred at a dose of 2.0 ml/kg.

S-5: No deaths resulted from a dose of 5.0 ml/kg, but the animals evidenced incoordination during and immediately after exposure.

S-6: No deaths or signs of toxicity resulted from a dose of 5.0 ml/kg.

7. *Repeated Skin Irritation*

By the sixth day of application, all of the samples had produced varying degrees of erythema and, in most instances, eschar formation. Treatment was discontinued upon appearance of eschar, but daily readings were continued. All compounds produced eschar in at least one half of the test animals.

DISCUSSION

All of the samples tested may be classified as practically nontoxic or relatively harmless when administered orally, with the exception of A-2 which should be considered slightly toxic. The aromatic content definitely influences the degree of toxicity: the four aromatic samples have LD_{50} values below 15 ml/kg while the remaining samples, all essentially aromatic-free, have LD_{50}'s above 25 ml/kg.

The percutaneous toxicity was also affected by aromatic content. All four aromatic samples caused partial mortality at 5.0 ml/kg, while the aromatic-free materials caused no deaths at this level, with the exception of S-4 which did cause partial mortality. In the skin and eye irritation tests, the aromatics generally caused more pronounced irritation (usually moderate in degree) than the aromatic-free products. This distinction could not be made for vapor toxicity since the samples varied widely in vapor pressure.

Acute intoxication was most commonly characterized by depression. Animals that received doses orally, percutaneously or by inhalation, became uncoordinated, prostrate or comatose at doses that produced partial mortality, often at doses that were not lethal. Convulsions were occasionally seen in the rats and were generally fatal. Practically all of the samples produced toxic symptoms or mortality by one or another of the routes of administration, with the exception of S-6 whose toxicity was negative in all tests except that of aspiration hazard. The majority of samples also produced local irritation when applied percutaneously.

Two of the samples, A-4 and S-6, were selected for aspiration hazard testing. Despite their low systemic toxicity, both produced marked lung irritation and death. The fact that even these solvents proved hazardous indicates that the other solvents with equal or lower viscosity would produce similar or worse effects. Sample S-6 was similar in action to the positive control, kerosene, killing half the animals, and producing greatly increased lung weights in the survivors. Sample A-4 also killed half of the animals, but death occurred more rapidly, and lung weights of survivors were not increased as much.

All of the samples tested caused moderate to severe skin irritation upon repeated application. Sample S-5 was the least irritating. No pattern of irritation correlated to aromatic content was evident in the repeated application tests.

SUMMARY

Toxicologic studies were conducted on ten samples representative of the type of compounds present in various commercial hydrocarbon solvents. As judged by oral toxicity, the samples ranged from slightly toxic to relatively harmless. Vapor toxicity was also slight; saturated vapors of the majority of products were not toxic at room temperature. The two samples tested for toxicity after aspiration were both hazardous as rated by the method of Gerarde.[5] Percutaneous toxicity tests

indicated that all samples were practically non-toxic by this route. Primary skin irritation ranged from moderate to minimal, as did eye irritation. All of the samples tested produced moderate to severe skin irritation upon repeated application. In general, the aromatics were more toxic and irritating than the saturated hydrocarbons.

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