



PROCEEDINGS OF THE SYMPOSIUM

ON

INDUSTRIAL SOLVENTS

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## PETROLEUM HYDROCARBON SOLVENTS

Robert A. Scala, Ph.D. \*

The name most closely associated with the toxicology of petroleum hydrocarbons is that of Horace W. Gerarde. Dr. Gerarde was killed prematurely in a plane crash in Turkey about two or three weeks ago. In fact, a memorial service will be held for him on Saturday of this week. I have known Dr. Gerarde since I entered the field of toxicology and our careers at **Esso** overlapped for about a year. Out of respect for his memory and his contribution to what is known about the toxicology of petroleum hydrocarbons, in my own small way, I would like to dedicate this particular paper.

It is impossible in the time that I have available to me to discuss all that is known about the toxicology of petroleum hydrocarbons. It is like talking about the toxicology of chemicals or the toxicology of plastics. So in the next 30 minutes or so I would like to describe a program which is now in its sixth year at the Bushy Run Laboratories of Mellon Institute, Carnegie-Mellon University sponsored by the petroleum industry. This work will be published by Dr. Carpenter and his colleagues there. The data which are emerging, I think, will be of interest to all of us. The work was sponsored and is continuing to be sponsored by the petroleum industry at large.

Now the first question is raised: "Why bother to have an industry-wide program?" The first slide is a representation of what we believe to be the justifications for industry-wide support, at least in our industry, for toxicological studies. First of all, few materials are novel in the petroleum industry. In the petroleum industry are quite limited resources in the discipline of toxicology. There aren't very many toxicologists. Very few of the companies, have their own toxicology laboratory. The increasing and unending demands for research on the evaluation of safety are so extensive that no one company can afford to do everything that has to be done. Finally, the influence of, what I politely call "non-scientific elements" on the scope and design of the research programs is best met on the broadest possible base. There is always a question of credibility and we feel that by having a broadly funded, broadly operated, broadly scrutinized program, we can meet certain of their objections.

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The history of the program is as follows: In the Spring of 1968, the Subcommittee on Toxicology of the American Petroleum Institute (that's the trade association which I will be referring to as API) began putting together a research program on solvents for several reasons. First of all, there really were no good toxicity data on petroleum solvents since the time B. C. --that's before chromatography. The work of Lehmann, Flury, and Zernik, and several other pioneer investigators was all concentrated, for the most part from 1928 to 1932. There had been additional scattered publications in the literature, but we felt that there was no sound data base. Along with this, the Threshold Limit Values (TLV's) for petroleum compounds were perhaps set on something other than a strong data base; many of them by analogy, many of them based on quite limited work. The Committee did the best it could with what it had to work with. The idea that petroleum products are safe because they have had a long history of safe use is what we call "anecdotal". That is, the plant nurse declares, "We have never had anybody injured!". Or someone says, "We have been using this solvent for 30 years in our plant and we have had no problems." In most people's opinion, that is no longer a satisfactory measure of the safety of a material.

There are newer concepts in setting threshold limit values. It's no longer a matter of whether the worker can be exposed eight hours a day, five days a week, for an indefinite work time without falling dead, or being injured in some way that is immediately apparent. The newer concepts involve nuisance, odor, discomfort, perhaps even biochemical changes. These are things that Dr. Stokinger and his TLV committee are wrestling with each time they meet. We all know that threshold limit values are being incorporated into legislation and into various operating codes, and the API would like to see those numbers, if they are going to be incorporated, established on the soundest possible basis. We anticipated in 1968 that we would have occupational health and safety legislation, which, in fact, we do.

Finally, the industry is trying to take a responsible position. (Slide 2) Dr. Golz, the former Medical Director of the American Petroleum Institute, expressed in 1968 the essence of why we are doing what we are doing. "In the absence of soundly based toxicological and exposure data, industry is faced with the likelihood of being regulated by unnecessarily restrictive standards arbitrarily established without sound scientific foundation. It is believed that the petroleum industry can play a role in the establishment of the standards by which it will be regulated if it is willing to undertake promptly an organized long-range program of toxicological investigation of its products." That gentlemen, is really why I am standing here today. To give you the first fruits of that commitment. It is a continuing commitment. It has been an expensive one.

(Slide 3) I want to now acknowledge the associates that I have had in this program. This is the API's Committee on Toxicology at the time this program was first established. I merely wish to acknowledge formally their continued support and participation. (Slide 4) For purposes of organization of our program, we have set up a certain number of research panels. This is simply to show you how we have subdivided our tasks to look into things. The first panel is the one which has been concerned with the work I will talk about for the most of the rest of my time.

(Slide 5) Those of you who have students know that it is always good to start them out in an experiment with a statement of objectives. Why are we doing this research? So the objective of this experimental program is to define the toxicity of petroleum products. We also have as an objective, recognition of our responsibility to carry out a proper program--that the industry does have responsibility for the safety of its products. The emphasis, initially, in this program, was on materials under review by the TLV Committee. Later on, we selected materials on the basis of commercial usage, availability of data, and occupational health needs,

Two other things need to be pointed out. We excluded benzene and motor fuels from this program as we have separate research studies on those two products. Early we established what we believe to be satisfactory interaction with the TLV Committee and that interaction has continued. They see all the data as soon as we see it. The approach to this program was several-fold. First of all, we wanted to identify materials of interest for study, then we wanted to characterize the chemical composition of the products selected. We felt we would characterize toxicity, which is different from determining hazard. We are going to characterize toxicity through a study of acute and subacute effects in animals, and limited study in man. Finally, we hope to develop techniques for correlation, prediction of potential effects, and/or safe exposure levels.

Our initial question was what determines the toxicity of a petroleum hydrocarbon? Are there any physical characteristics or other properties that might be clues to the toxicity of the material? We thought boiling range and aromatics content would be critical determinants of toxicity. There was some precedent for this in the literature. To relate these items in order to allow us to do meaningful experiments and avoid repetitious experiments as well as identify toxicologically important compositional matters needs a matrix approach.

(Slide 6) Our matrix was simply a graph to relate total aromatics content in per cent and boiling range in degrees F. We could put as a point on that matrix each solvent we wanted to study. We could there-

fore identify critical areas of zones, and also avoid doing what we would consider to be repetitious experiments.

(Slide 7) These are the basic animal experiments which we are doing on these solvents and include the acute LC<sub>50</sub>. We use rats and we expose them for four hours. We then did a simple acute inhalation study using cats and dogs. These were also four hour exposures. The final acute test simulated a massive over-exposure. Rats were exposed at a significant level above the LC<sub>50</sub> for a short period. Finally we carried out a conventional subacute inhalation study for six hours a day, five days a week, for 13 weeks using rats and dogs at graded levels.

We also did a challenge acute exposure on a certain number of these animals after they had been through this 13-week exposure regimen. These animals, plus some animals which had never been exposed before were given a brief, high level exposure to determine whether or not there was any hardening or any increased sensitivity. We measured the time to death, because we gave them a very high dose. If the animals which had been exposed for 13 weeks died earlier, their exposure had rendered them more sensitive. If they died later, their exposure had rendered them less sensitive.

Out of 14 materials which we have studied, we have seen one instance of hardening, that is lowered sensitivity, as the result of prior exposures and no instances of increased sensitivity.

Finally, we did respiratory tract irritation tests, an excellent predictor of respiratory irritation in man.

(Slide 8) The human protocol included two experiments. One was odor perception and the other was sensory irritation. The numbers of subjects are small, fewer than 10. We didn't realize at the time how important these experiments were. I think it will become apparent as I work my way through some of the data.

(Slide 9) These are the results of the experiments which were carried out in the first year of the study. We studied three solvents, VM & P Naphtha, Stoddard Solvent and Rubber Solvent. These are common solvents in the industry and they have relatively low aromatics content. The term "hygienic standard" is employed by our contractor, Mellon Institute of Carnegie-Mellon University is their interpretation of their findings. Incidentally, this was a "hands off" experiment. We gave the contractor guidance, and counsel, but the data and the interpretations are theirs. "Hygienic standard" is their evaluation of an acceptable industrial exposure level. These data are the property of the people carrying out the experiments. Manuscripts have been prepared

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and are in the process of being submitted to the journal Toxicology and Applied Pharmacology.

The hygiene standards have been expressed as parts per million and milligrams per liter. The chamber measurements are based on milligrams per liter of material which was converted by means of an average molecular weight to parts per million. The parts per million figures given in the data tables are derived figures. The milligrams per liter figure is a laboratory measured figure.

For **V M & P** naphtha, the hygienic standard was based on the human studies. There was a human sensory response at a lower level than in the animal studies. For Stoddard Solvent, it was the animals that were the **more sensitive**. For Rubber Solvent, the 800 parts per million figure is based on the human response,

(Slide 10) Now we get into the 1970 ~~study~~. The first thing to be explained is the terms that we used. Mixed xylene **is** one which is common to you, just like the three names on the previous slide. 60 Solvent, 70 Solvent, 140 Flash Aliphatic are what we call trivial names. These are names which we have used within the program to identify these solvents. First of all, because we don't know who supplied them, ~~therefore we~~ don't know the actual trade name **for** those specific materials. Secondly, because there is no generally accepted trade name within the entire industry. The numbers generally bear some relationship either to flash point, as in the latter case, or to the kauri-butanol number.

The **Mixed Xylene** standard is 230 parts per million, one milligram per liter, based on the human work. The 60 Solvent figure is **.45** milligrams per liter (90 parts per million) and that is based on animal work. That one has the biggest question mark of any of our work. The 70 Solvent standard **is** 100 ppm (0. **54** mg/l) based on both human and animal work. The standard for 140 Flash Aliphatic is 37 ppm (0. **23** mg/l) and it is based on the maximum obtainable concentration. This illustrates the third criterion for selecting the hygienic standard. 140 Flash Aliphatic solvent has such low vapor pressure that it was not possible to achieve a vapor concentration high enough to cause any effects in either the animals or in man. The standard is therefore, the maximum obtainable concentration. This standard simply reflects the maximum obtainable vapor concentration. One could generate a more concentrated test atmosphere, even as a vapor, but it is no longer 140 Flash Aliphatic Solvent. Again, the ground rule was to achieve **as** high a vapor concentration as possible, and still have the vapor composition the same as the liquid composition. Any higher temperature, in effect, distilled **off** the light ends of the solvent.

(Slide 11) 80 Thinner and 50 Thinner are trivial names, and the hygienic standards are 150 ppm (.65 mg/l) and 430 ppm (1.7 mg/l), respectively. The human studies on deodorized kerosene have been completed and the maximum obtainable concentration (.11 milligrams per liter, 16 parts per million) seemed to be the limiting factor. The standards are in brackets because they are still tentative.

(Slide 12) For toluene concentrate the tentative figure is 1.9 mg/l, (488 ppm), again based on human studies. Toluene concentrate is almost 50% toluene and the standard is at some variance with the TLV for toluene. The standard for 40 Thinner is 22 mg/l, (36 ppm). These are tentative values because the final report has not been issued. The high aromatic solvent work is still in progress.

(Slide 13) Another element began to emerge as a possible responsible factor for toxicity besides boiling range and aromatics content and that is the "naphthene" content. Naphthenes are cycloparaffins. I am not talking about naphthalene, the condensed ring aromatic, but "naphthenes" which are, saturated ring structures. To challenge this proposition a naphthene experiment was devised using High Naphthenic Solvent, Naphthenic Aromatic Solvent, and Nonane, which is purely paraffinic. The three solvents have the same boiling range and varying naphthene content: 0, 40%, 70%. As reference materials, Stoddard Solvent and 70 Solvent were used. This may be viewed as extending the matrix into three dimensions.

(Slide 14) On this slide are noted the various materials which were studied. The texture of the stripe underneath just identifies the year of the study. The length of the stripe, however, is critical, and covers the boiling range for the material. As examples, item D which is Mixed Xylene, and item M, which is the Toluene Concentrate, are fairly narrow bands because they are relatively narrow boiling materials and have relatively few isomers present. Stoddard Solvent is a much more complex mixture, covering a far larger number of hydrocarbons over a broader boiling range. Is there some way to cover that chart with a series of bands or zones which will indicate, based on aromatics content and boiling range, what the TLV should be?

(Slide 15) This is the result. Materials to the left of the line, appear to have hygienic standards of greater than 200 parts per million, (greater than 1 milligram per liter). Materials to the right of the zig zag line appear to be below 200 parts per million (below 1 milligram per liter). Low boiling solvents regardless of their aromatics content have relatively high hygienic standards. At a given aromatics content in the bottom third an increase in boiling range results in a decreased hygienic standard. The zig zag line is simply a question of volatility and

not a toxicological issue. A low hygienic standard such as for 140 Flash Aliphatic and Deodorized Kerosene, is based on the maximum obtainable concentration. So the bottom right is a zone in which volatility is a limiting factor, not toxicity or irritancy to humans. The upper right is an area where high boiling materials or high aromatics are both operating to keep the hygienic standard on the low side of this group of solvents. So to a degree, based on present knowledge, boiling range and aromatics content do seem to determine the final hygienic standard, even if they don't really determine toxicity. The issue is still open because we have not fully resolved the naphthene question, the third dimension on the slide.

But we have some tentative conclusions to be shared with you. For low boiling materials, aromatics content doesn't seem to make a difference, and the materials have relatively high hygienic standards. There does not seem to be a tremendous need for exposure control based on these studies. For high boiling materials of low aromatics content, the volatility seems to be the limiting factor, and therefore, the hygienic standards will be **low**, but they will be low because of volatility, not because of toxicity. And for materials which are either high boiling or with significant aromatics, (the top right **hard** area) lower hygienic standards and greater control, seem to be indicated.

(Slide 16) **This** is another experiment being done for **API** by Dr. Charles Hine of Hine laboratories and involves mutagenicity testing. Mutagenicity is not confined to females; it is also potentially a problem in males, so dominant lethal tests were performed. There is no statistically significant difference between controls and test animals in terms of dominant lethal effect, which is one of the current measures of mutagenicity. Additional work related to genetic effects is planned for three of the solvents: Rubber Solvent, **60** Solvent, and the High Aromatic Solvent, in a cytogenetic test. That's a quick over-view of our ongoing program.

JUSTIFICATION FOR INDUSTRY-WIDE  
SUPPORT OF TOXICOLOGICAL RESEARCH

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Slide 1

- \* Few materials are novel
- \* Resources in this discipline are limited
- \* Increasing and unending demands for research on evaluation of safety are **so** extensive that no one company can afford to undertake the burden
- \* Influence **of** nonscientific elements on scope and design of research programs is best met on broadest possible base.

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Slide 2

In the absence **of** soundly based toxicological and exposure data, industry is faced with the likelihood of being regulated by unnecessarily restrictive standards arbitrarily established without sound scientific foundation. It **is** believed that the petroleum industry can play a role in the establishment of the standards by which it will be regulated if it **is** willing to undertake promptly an organized, long-range program **of** toxicological investigation of its products.

H. H. Golz  
April 16, 1968

API - SUBCOMMITTEE ON **TOXICOLOGY**

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**Slide 3**

|                                  |                                   |
|----------------------------------|-----------------------------------|
| E.R. Averill - Mobil             | <b>W.E.</b> Rinehart - Ethyl      |
| R. W. Call - Union               | R.A. Scala - <b>Esso</b> Research |
| <b>I.T.</b> Fritz - Consultant   | H. W. Spies - American            |
| J.M. McNerney - API <b>Staff</b> | J.J. Thorpe - <b>Exxon</b>        |
| C.F. Reinhardt - Dupont          | <b>A.S.</b> Todd - Sun            |

API - SUBCOMMITTEE ON TOXICOLOGY

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**Slide 4**

- \* Panels
  - Matrix studies - Rinehart, Spies
  - Metabolism - Todd, Reinhardt
  - Human Sensory Response - Averill, Spies
  - Mutagenicity - Call
  - Histopathology - Thorpe
- \* Liaison
  - National Clearinghouse for poison control centers - Spies
  - Ansi** 2-66 Committee on prevention and control of hazards to children - Averill

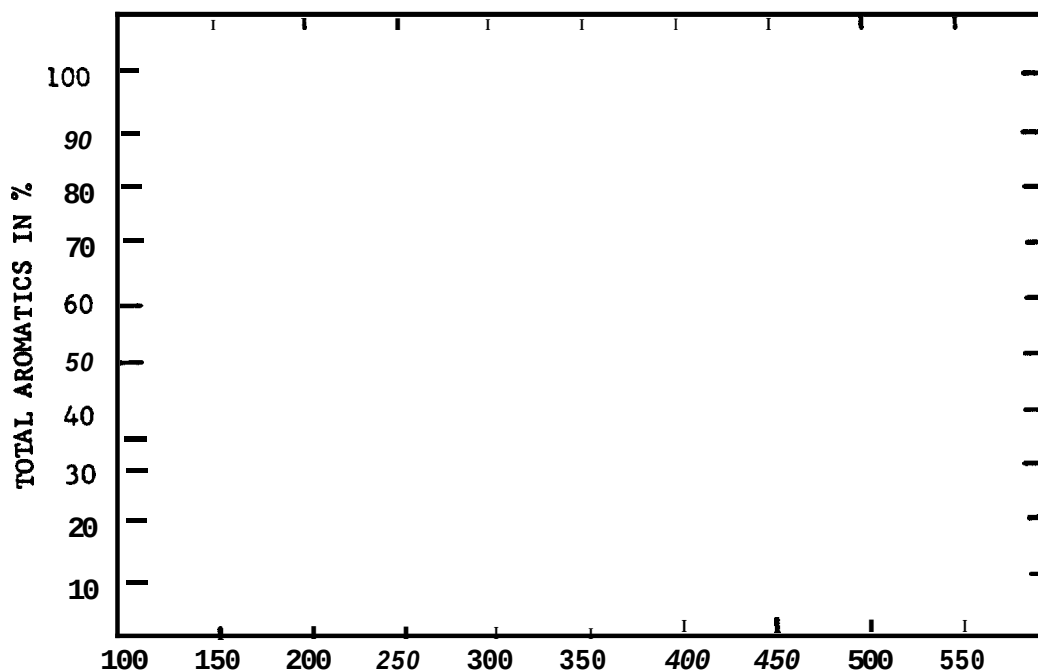
**OBJECTIVE AND IMPLEMENTATION**  
**API - HYDROCARBON TOXICITY PROJECT**

Slide 5

- \* Objective - Define toxicity of petroleum hydrocarbons
- \* Emphasis - Initially, materials under review by TLV Committee  
Later, materials selected on basis of commercial usage, availability of data, occupational health needs
- \* Approach - Identify materials of interest for study  
Characterize chemical composition  
Characterize toxicity through study of acute and subacute effects in animals, limited study in man  
Develop techniques for correlation and prediction of potential effects and/or safe exposure levels.

Slide 6

**PETROLEUM HYDROCARBON TOXICITY MATRIX**



BASIC PROTOCOL - HYDROCARBON TOXICITY PROJECT  
ANIMAL STUDIES

Slide 7

| <u>Test</u>            | <u>Species/Number</u>                     | <u>Duration</u>                    | <u>Purpose</u>                                         |
|------------------------|-------------------------------------------|------------------------------------|--------------------------------------------------------|
| Acute LC <sub>50</sub> | 15 Rats/ Level                            | 4 hours                            | Define acute toxicity                                  |
| Acute Inhalation       | 4 Cats - 1 level<br>Dogs - Several levels | 4 hours                            | Species comparability                                  |
| Massive Acute          | 5 Rats at 5x LC <sub>50</sub>             | 5-15 min.                          | Determine effects of acute overexposure                |
| Subacute Inhalation    | 25 Rats and 4 dogs per level              | 6 hours/D.<br>5 D. /WK.<br>13 WKS. | Effects of repeated exposures at graded concentrations |
| Challenge Acute        | 10 Rats/Level                             | 6 hours                            | Measure changes in susceptibility                      |
| Respiratory Irritation | 6 Mice/Level                              | 1 minute                           | Simulate human response                                |

\* Histopathology and statistical analysis done in all tests

BASIC PROTOCOL - HYDROCARBON TOXICITY PROJECT  
HUMAN STUDIES

Slide 8

| <u>Test</u>        | <u>Duration</u> | <u>Purpose</u>                                                                |
|--------------------|-----------------|-------------------------------------------------------------------------------|
| Odor Sensation     | 5-10 seconds    | Determine Concentration at which odor is detected (not identified)            |
| Sensory Irritation | 15 minutes      | Determine concentration at which eye, nose, and throat irritation is detected |

API - HYDROCARBON TOXICITY PROJECT  
1969 STUDY

Slide 9

| <u>Material</u>  | <u>Boiling Range</u><br>°F | <u>Aromatics</u><br>% | <u>Hygienic Standard</u> |            | <u>Basis</u> |
|------------------|----------------------------|-----------------------|--------------------------|------------|--------------|
|                  |                            |                       | ppm                      | mg/l       |              |
| VM & P Naphtha   | 250 - 300                  | 10                    | <b>400</b>               | 2.0        | <b>H</b>     |
| Stoddard Solvent | 300 - <b>380</b>           | <b>20</b>             | <b>200</b>               | 1.2        | <b>A</b>     |
| Rubber Solvent   | 170 - 230                  | <b>&lt;5</b>          | <b>800</b>               | <b>3.2</b> | <b>H</b>     |

BASIS: H = Human Sensory Response; A = Animal Pathology

API - HYDROCARBON TOXICITY PROJECT  
1970 STUDY

Slide 10

| <u>Material</u>                | <u>Boiling Range</u><br>°F | <u>Aromatics</u><br>% | <u>Hygienic Standard</u> |             | <u>Basis</u> |
|--------------------------------|----------------------------|-----------------------|--------------------------|-------------|--------------|
|                                |                            |                       | ppm                      | mg/l        |              |
| Mixed Xylene                   | 280 - 290                  | 100                   | <b>230</b>               | 1.0         | H            |
| 60 Solvent                     | <b>260</b> - 320           | <b>50</b>             | 90                       | 0.44        | <b>A</b>     |
| <b>70</b> Solvent              | <b>320</b> - 410           | <b>65</b>             | 100                      | <b>0.54</b> | H, A         |
| 140' <b>Flash</b><br>Aliphatic | <b>360</b> - 410           | <b>&lt;5</b>          | <b>37</b>                | <b>0.23</b> | MC           |

BASIS: H = Human Sensory Response

A = Animal Pathology

MC = Maximum Attainable Vapor Concentration

API - HYDROCARBON TOXICITY PROJECT  
1971 STUDY

Slide 11

| <u>Material</u>        | <u>Boiling Range</u> | <u>Aromatics</u> | <u>Hygienic Standard</u> |             | <u>Basis</u> |
|------------------------|----------------------|------------------|--------------------------|-------------|--------------|
|                        | <u>°F</u>            | <u>%</u>         | <u>ppm</u>               | <u>mg/l</u> |              |
| 80 Thinner             | 210 - 290            | 70               | 150                      | .65         | <b>H</b>     |
| 50 Thinner             | 210 - 220            | 30               | 430                      | 1.7         | <b>H, A</b>  |
| Deodorized<br>Kerosine | 410 - 520            | c5               | (16)                     | (.11)       | MC           |

BASIS: H = Human Sensory Response

A = Animal Pathology

MC = Maximum Attainable Vapor Concentration

Data in Brackets are tentative and subject to change.

API - HYDROCARBON TOXICITY PROJECT  
1972 STUDY

Slide 12

| <u>Material</u>          | <u>Boiling Range</u> | <u>Aromatics</u> | <u>Hygienic Standard</u> |             | <u>Basis</u> |
|--------------------------|----------------------|------------------|--------------------------|-------------|--------------|
|                          | <u>°F</u>            | <u>%</u>         | <u>ppm</u>               | <u>mg/l</u> |              |
| 40 Thinner               | 370 - 450            | 20               | (36)                     | (0.22)      | MC           |
| Toluene<br>Concentrate   | 200 - 230            | 45               | (480)                    | (1.9)       | H            |
| High Aromatic<br>Solvent | <b>365</b> - 400     | N. A.            | <b>N. A.</b>             | N. A.       |              |

BASIS: H = Human Sensory Response

MC = Maximum Attainable Vapor Concentration

N.A. = Not Available

Data in brackets are tentative and subject to change

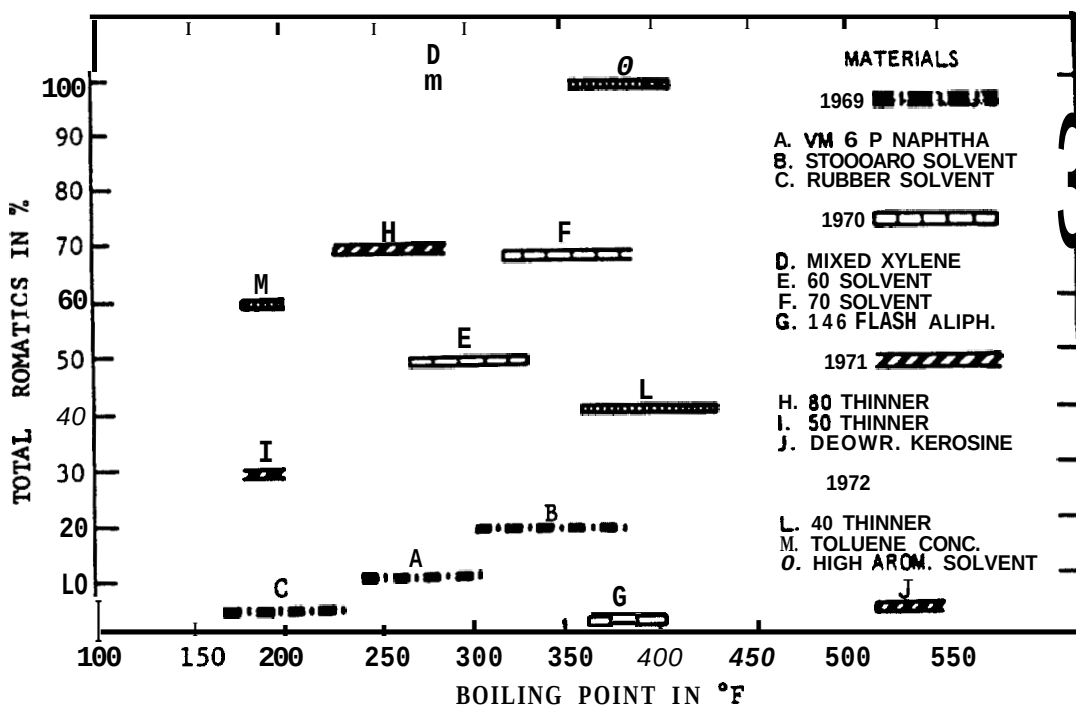
# API - HYDROCARBON TOXICITY PROJECT 1973 MATERIALS

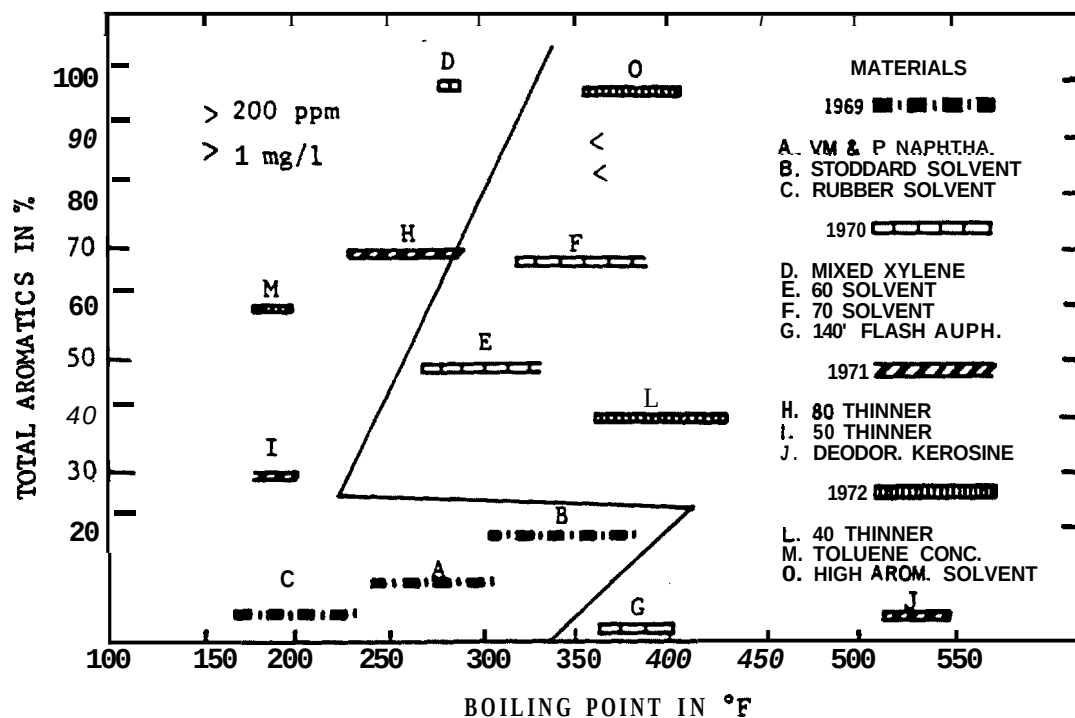
## Slide 13

| <u>Material</u>             | <u>Paraffin Naphthene Aromatics</u><br><u>%, Approx.</u> |    |    | <u>Boiling</u><br><u>Range</u><br><u>°F, Est.</u> |
|-----------------------------|----------------------------------------------------------|----|----|---------------------------------------------------|
| <b>Selected</b>             |                                                          |    |    |                                                   |
| High Naphthenic Solvent     | 28                                                       | 71 | 1  | 300 - 400                                         |
| Naphthenic Aromatic Solvent | 22                                                       | 41 | 37 | 300 - 400                                         |
| Nonane                      | 100                                                      | -- | -- | 300                                               |
| <b>Reference</b>            |                                                          |    |    |                                                   |
| Stoddard                    | 40                                                       | 41 | 19 | 300 - 375                                         |
| 70 Solvent                  | 16                                                       | 16 | 68 | 320 - 410                                         |

## Slide 14

### PETROLEUM HYDROCARBON TOXICITY MATRIX





## MUTAGENICITY TESTS - HINE LABORATORIES

### Slide 16

Test - Dominant Lethal (nonviable Mutations)

Species/Dose - Rats and Mice - 1 ML/KG

Criteria Evaluated - Fertility (% Pregnant)

$$\text{Mutagenic Index} = \left( \frac{\text{Fetal Mortality}}{\text{Total Implants}} \right) \times 100$$

Conclusions

No Mutagenic activity

Any effect on fertility would be marginal

Marginal effect on fertility possible