

AMERICAN PETROLEUM INSTITUTE
Medicine and Biological Science Department
Toxicology Committee
Minutes of Meeting

Marriott Hotel
San Diego, California

Wednesday, January 11, 1984
9:00 a.m.

ATTENDANCE:

J. A. MacGregor, Ph.D. - Chairman
P. H. Craig, V.M.D. - Vice Chairman

Committee Members Present

W.D. Broddle	R.W. Mast
C.C. Conaway	A.E. Mekitarian
C.R. Clark	R.N. Roth
E.M. Coomes	C.A. Schreiner
B.J. Garvin	M.B. Slomka
A.A. Halder	F.B. Thomas
E.A. Kuna	W.C. Thomas
M.L. Lakin	C.O. Ward
A.C. Lewis	

Others Present

H.C. Blum	H.N. MacFarland
E. Golberg	S.S. Sternberg

Staff Present

C. Blank	K.A. Hazer
S.T. Cragg	C.E. Holdsworth

1. OPENING REMARKS

Chairman J.A. MacGregor opened the meeting by welcoming those present, including the SPAR consultants, Drs. Leon Golberg and Steven Sternberg. She advised that annual project proposal sheets for 1985 would be sent soon from staff and that the members should give careful consideration to prioritizing the projects. In order that the

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process run smoothly, Dr. MacGregor further recommended that each company's HESC representative be closely involved or at least advised of their company's prioritization. This would help insure the successful implementation of the 1985 toxicology program.

In order to help the members prioritize the 1985 projects, HESC wants a balance of 3 areas of testing. These include: 1) issues (e.g., gasoline, benzene); 2) methods development; and: 3) basic information. Dr. Holdsworth added that it is not too late to submit research proposals for consideration in the 1985 budget.

The Toxicology budget is \$4.8 million for 1984 and the task forces are urged to move their projects along now in order to avoid a year-end rush to commit budgets. All but a small fraction of the 1983 budget of \$2.4 million was committed last year. This included PS-8 money which HESC would not allow expended while they were reviewing proposed studies under this project. This and synfuels money was therefore allowed to be carried-over.

II. SPECIAL REPORTS

A. Coordinating Committee on Gasoline (CCG)

Dr. Slomka reported that the OH-39 task force had visited Dr. Curtis Wilson of Scripps Institute just a few days previously. This investigator will help the task force evaluate a population of gasoline abusers for immunological effects.

On behalf of the CCG, Dr. Slomka requested information updates from all toxicology task forces on gasoline. There is a trend toward more coordinating committees and Dr. Slomka recommended that more technically oriented individuals be appointed to them in the future.

Discussion turned to recently completed and ongoing toxicological research with gasoline. The proceedings of the Boston nephropathy workshop have been published by API and will be peer-reviewed for subsequent publication in hardbound copy in the Advances in Toxicology. The UAREP report is nearing finalization and should be available soon.

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It was decided that interim reports will be obtained from the contractor regarding the PS-53 "time-course" gavage study. The final report is expected midyear.

B. Benzene

P.J. Garvin reported on the status of talks between the union and industry on a benzene standard. This activity is being sponsored by OSHA which is scheduled to issue the standard in June of this year. Mr. Garvin said that, thus far, talks have focused on ancillary issue, steering away from a PEL.

Regarding EPA activities, the proposed benzene standard for maleic anhydride plants has been withdrawn under stationary sources regulation. However a standard is expected for coke plants and a NESHA for refineries will be forthcoming. Mobil sources may be regulated in the future.

A CMA sponsored—epidemiology study has recently been completed, C.O. Ward reported. The results are equivocal and depend upon which control group is used for comparison. A cohort of concurrent controls was very healthy with no incidence of leukemia, far below the national average. Comparison to this group showed an excessive rate of leukemia in the exposed workers, which when compared to the national average appeared conversely, to have normal incidence rates of this disease. Curiously, no cases of acute myelogenous leukemia occurred in the exposed workers.

C. Asphalt

F.B. Thomas related that IARC would complete its review of asphalt (bitumens) by the end of February. API has been invited to send one participant in the review proceedings (not yet chosen). Barry Simpson of Shell International will participate on behalf of CONCAWE while Ted Chipperfield, consultant retiree from IP will provide chemistry expertise to the IARC review panel.

The asphalt consortium of trade associations is reviewing a finalized draft of 2 monographs dealing with asphalt (one on chemistry and another on biological effects). Further revisions will be sought, Dr. Thomas added.

The consortium is also conducting a feasibility evaluation for a possible epidemiology study, W.D. Broddle said. A Dr. Chaizze of Georgetown University has been contracted to perform the feasibility analysis. Dr. Broddle also updated the committee on the status of the NIOSH sponsored skin-painting studies which are to be conducted at A.D. Little.

Regarding the A.D. Little study, samples are now being prepared and the protocol generated. The study will encompass 50 groups exposed to variously generated asphalt and subfractions thereof. Chemical analysis may be done directly by NIOSH. NIOSH will sponsor a symposium, Dr. Broddle continued, which is intended to generate guidelines for biological monitoring. It can be concluded from all this NIOSH activity that asphalt is of high concern. Furthermore, substantial litigation against the industry is occurring where workers are claiming to have suffered health effects from asphalt exposure.

D. Hydrocarbons (Gasoline) in Groundwater

Dr. F.B. Thomas related that MBSD had initially requested assistance in identifying which chemicals might be present (and in what concentrations) in groundwater contaminated by gasoline and other hydrocarbons. From this request, a multidisciplinary group was formed under EAD which is evaluating the solubilities at different temperatures of those chemicals likely to be present. Company records reveal that benzene, toluene, xylenes, methyl tertiary-butyl ether, tertiary-butyl alcohol and ethyltoluene are present at concentrations and in proportions which depend upon their water solubility, the distance from the contamination and a variety of other factors. Dr. Thomas added that MBSD is currently acting in an advisory capacity but may become more active later if testing is needed. TRC has been contracted to conduct a literature survey on the potential health-effects of contaminated groundwater and may perform experiments to model the plume of a gasoline spill. Aside from the obvious question of oral ingestion of contaminated water, Dr. Thomas noted that some of the issues which are being evaluated include: 1) whether food can be washed with contaminated water; 2) whether such water can be used for bathing and; 3) whether boiling increases or reduces contaminant concentrations. Dr. MacGregor added that it is most important that the interdisciplinary

group not fall behind schedule in light of the importance of the contaminated water issue and because possible future MBSD health related research hinges upon the conclusion reached by the group.

Dr. MacGregor said that the Toxicology Committee should be ready when this group defines what to test by having tox studies identified and protocols generated by the time samples become available. Dr. Thomas will poll Toxicology Subcommittee chairs to compile a list of needed studies.

E. TSCA Section 4 Activities

API has formed a group in response to EPA's new program: Leaking Underground Storage Tanks (LUST), which is attempting to evaluate the extent of underground storage tank leaks and associated problems, R.N. Roth reported. EPA is presently evaluating the ability of the industry to comply with a range of standards which it is considering.

Finalized GLP's have been issued by EPA in Vol. 48, page 53946 of the Federal Register, Dr. MacGregor noted. It is possible to submit comments on these standards annually. B.K. Hoover (API/MBSD staff) is coordinating the first round of responses for the industry and those interested should submit their comments to her. Dr. MacGregor said that the new guidelines call for detailed chemical analysis of test samples even for acute tests. Even while responding to some of the items which appear unreasonable, it was agreed that API would try to comply with the new guidelines in future toxicity testing. In a related area, several members noted that their studies had been audited by EPA, either in their own laboratories or in a contractor's. EPA seems to be stepping up its activities in this area and has become more sophisticated in the auditing process.

The Interagency Testing Committee (ITC) recently issued a list of 82 chemicals and API/HSRD will supply comment. Oleolamine is on the list and is of interest to the industry because of its presence in lube oils. Drs. Craig and Daikin recently made a presentation to the ITC to argue against testing individual components of complex mixtures in order to predict the toxicity of the whole. The presentation seemed to be well received.

Dr. Roth related that API/ HSRD has made comment to EPA's proposed test rule on ethyltoluene (ET) and trimethylbenzene (TMB). API has argued that EPA should not hold the petroleum industry liable for testing these compounds on the basis that they occur to a few percent in gasoline (and because great quantities of gasoline are sold, the petroleum industry thus indirectly becomes the largest producer of these chemicals). API has also argued (similar to the ITC presentation), that individual tox testing results from these two compounds will not be useful in predicting the toxicity of gasoline which is comprised of at least 300 chemicals. It is estimated that perhaps one year may pass before EPA makes a decision on this issue. Therefore, the Toxicology Committee may not be asked to perform studies for this length of time (or ever) on ET, TMB or even a C-9 cut which EPA might be willing to substitute as more representative of gasoline. Specifically regarding C-9 cuts, the Interagency Testing Committee has recommended to EPA that additional toxicology information is needed. M.B. Slomka indicated that cuts with high levels of C-9 aromatic compounds have long been used in great quantity as vehicles for pesticides.

EPA has also become interested in cresols, Dr. R.W. Mast related. Because cresols occur in gasoline, another test rule may be issued affecting the petroleum industry on the same basis as that for ET and TMB. Dr. Mast noted that an interindustry "Cresols" task force exists which was negotiating with EPA on a voluntary testing program. Negotiations have broken down although some of the task force members are still trying to obtain funding. Dr. Broddle added that several genetic tox studies have been completed on an equal mixture of o, m and p-cresols, some of which were positive.

F. Methyl tertiary-Butyl Ether

Dr. Conaway provided a written summary of this project as well as an oral presentation (Attachment I). The participants in these studies are considering whether to perform pharmacokinetic studies with remaining funds of \$28,000. Dr. Curtis Klaassen and an investigator at Naylor-Dana Institute are being considered for these studies. Dr. Golberg mentioned that Dr. Caldwell of St. Mary's Hospital in London is also highly qualified to perform such research.

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II. RESEARCH PROGRAM

Dr. Craig introduced the research report portion of the meeting, asking task force chairs from Physiological Responses to lead off.

A. Physicological Responses

1. PS-23: Immunology

Reporting for J. Butala, Dr. Broddle indicated that research is currently underway to assess possible differences in immunological effects of carcinogenic and noncarcinogenic polynuclear aromatic hydrocarbons. This research is taking place in the laboratory of Dr. Albert Munson of the Medical College of Virginia. Benzo(a)pyrene and benzo(e)pyrene are the model PNA's used and differences between these compounds have been observed in a number of immunological parameters when injected intraperitoneally into B6C3F1 mice. Multiple immunological tests are being validated during the course of this research.

The Task Force is planning to assess the effect of hydrocarbons on the immunological defense system of test animals by determining whether such chemicals alter the response to a viral or bacterial insult. Dr. Broddle added BaP and BeP will be used in this effort as well.

2. PS-29: Neurotoxicology

The task force is currently following-up on reports that prolonged exposure to high concentrations of toluene may be ototoxic. Using the auditory evoked response paradigm, researchers at SRI have observed a hearing decrement in the high frequency range of rats exposed to vapors of toluene at 1000 ppm 14 hour per day, 7 days per week, for 5 weeks. SRI believes that cochlear damage may account for the observations. Because of these studies and because of allegations that toluene may account for CNS damage in human solvent abusers, the task force

asked Peter Spencer of Einstein to cut additional CNS tissues from the previously conducted toluene neurotoxicity study to determine whether lesions were detectable in nuclei or neural tracts associated with hearing. This has been completed and results were negative. Einstein has been asked to expand the final report which was very brief. Since the cochlea of rats from the toluene study were not saved, it will not be possible to determine whether a specific effect in this organ has occurred. Thus, further studies may have to be undertaken to answer this critical question. The task force will visit SRI to evaluate their results and consider possible future research.

3. PS-32: Percutaneous Absorption

Mr. Garvin noted that research is being conducted with 3 investigators including Drs. I.H. Blank (Mass Gen. Hospital, Harvard), T.J. Franz (U of Washington) and H.I. Maibach (U. California).

Dr. Blank has measured the flux (ul/cm²/hr) through human cadaver stratum corneum of benzene liquid in various vehicles and as a vapor in air. Benzene vapor in air penetrates as well as the liquid, either in pure form or in a solvent vehicle. The task force will visit Dr. Blank in early February. Dr. Franz is also studying the skin absorption of benzene, reporting results as the percent of benzene absorbed. This investigator is inactive at this time regarding API research. Dr. Maibach has completed phase I which concerns method development and background determination of benzene in humans. However, he is still attempting to initiate his studies on ¹³-C benzene in humans. Mr. Garvin noted the conclusions stated in attachment from the work of all three investigators on benzene.

Dr. John Kao of Oak Ridge National Laboratory has recently received an API grant of \$100,000 to study the percutaneous metabolism of 1-2 ring aromatics, including benzene, and the effect of this metabolism upon absorption. C-¹⁴ labelled benzene will be studied in the skin of mice and other mammalian species, possibly including humans.

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4. PS-40: Behavioral Toxicology

In the recent past, classical neurotoxins were employed to produce discrete lesions (rather than generalized CNS effects) in an attempt to validate behavioral tests (including open field activity) for their sensitivity. Dr. Mast related that besides open field, the remaining two tests included, avoidance-response (shuttle box) and consummatory behavior. The open field test could distinguish treated from untreated animals at a dose level which was not detectable histopathologically two weeks after administration of a single i.p. dose (high dose: 2 mg/kg). Lab work has been completed, draft reports issued and reviewed, and the contractor is revising the final report. No further investigations are planned at this time.

A tutorial may be conducted for HESC on the possible need for neuro/behavioral testing by API. Dr. Scala is compiling a list of candidate presenters who are experts in this area and are outside the industry. There is also some interest in conducting an API-sponsored, 2-day workshop after the HESC tutorial, for industry scientists interested in the field. Finally, Dr. Lewis noted that the Grasso report on the human behavioral effects of light hydrocarbons is being reviewed. A critique of animal studies may be added to this predominantly clinical review.

5. PS-54: Human Bone Marrow Test Validation

Dr. Thomas reported that work is proceeding with Dr. J.H. Jandl of Harvard who is attempting to develop a human bone marrow culture system in which benzene and other hydrocarbons can be quantitatively introduced and their effect measure. This system has the potential to provide, in the case of benzene, direct information on the actual target organ affected in humans. Dr. Jandl will employ a Dexter medium in which a feeder cell layer is first established to provide the necessary microenvironment for the bone marrow precursor cells. After exposure to the test material, it is hoped that the system will be able to measure such endpoints as stem cell proliferating ability and stem cell viability, among others. Dr. Jandl is currently

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building his apparatus and establishing growth of the cells in the Dexter medium. The task force hopes to visit Dr. Jandl by the end of the first quarter of 1984, depending upon his progress.

B General Toxicology

1. PS-6: Motor Fuel Toxicity

This project is now in the final stages, Dr. Ward related. A final report has been issued which addresses those technical and quality assurance comments which the IRDC principal investigator deemed appropriate. Reasons for not incorporating other comments have been addressed in a separate letter from IRDC. The final report has been sent to the senior Toxicology Committee member from each participating company. Dr. Ward added that Dr. H. N. MacFarland has submitted a manuscript to the American College of Toxicology so that the results of the study may appear in the peer-reviewed literature.

2. PS-53: Motor Fuel Toxicity

Individual chemicals are being administered to rats in 28-day gavage studies in an attempt to identify chemical types responsible for inducing the acute nephropathy which is hypothesized to predispose male rats to renal carcinomas. Dr. Halder explained that the oral route had previously been found to induce the same acute renal lesion found in short-term inhalation exposures. The chemicals tested are shown in Attachment II-1 and II-2 and results are reported in II-3. As suspected, the branched alkanes are the most active. The study design is given in II-4. Currently, a time course study is being conducted on unleaded gasoline to adequately define this parameter (II-4/5). Next, several naphthas which usually comprise gasoline and several distillation cuts of gasoline will be tested in 90-day inhalation studies (II-6).

Regarding CIIT studies, in addition to Dr. Bus' work on metabolism and mechanisms of male rat nephropathy, Drs. Swenberg and Butterworth are considering initiation/promotion and mutagenesis tests, respectively. Information will be transmitted on a regular basis to a previously designated API/Tox-liaison group (Craig, Halder,

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Holdsworth, Lewis . API/QA will monitor the progress of the work on site.

3. PS-7: Benzene Toxicity

The activities of this task force are summarized in Attachment III-1. Dr. Ward added that the task force is currently considering extending preliminary work of Dr. Raymond Tice of Brookhaven. Dr. Tice has restained blood smears from the 5-day benzene inhalation pilot study to evaluate the incidence of micronuclei in the 2000 ppm and 0 ppm groups. This effort was successful. Now that the technique is validated, the task force may extend Dr. Tice's work to the 90-day study. In addition, the task force is evaluating another proposal from a Brookhaven researcher; Dr. Eugene Cronkite. Dr. Cronkite proposes to implant a diffusion chamber containing bone marrow into a host mouse which can then be exposed to benzene. The technique has the potential to use human bone marrow. Finally, the task force is re-evaluating the value of conducting a low-dose chronic benzene study (inhalation).

4. PS-22: Coke Toxicity

The in-life portion of a 2-year study on micronized, delayed process coke has been completed in rats and monkeys (Attachment IV-1). Dr. Halder added that results (limited histo for rats and only in-life for monkeys) are available through 18-months and a draft final report is expected soon which will incorporate the remainder of the study (IV-2/3). A previous in-life observation of ribcage "flaring" in monkeys has now been discounted by experts from the Primate Research Institute. Previous mutagenesis and dermal carcinogenesis results are summarized in Attachment IV-4.

5. PS-45: Refinery Streams Toxicology

Dr. Ward related that acute and subchronic toxicology studies are performed on generic refinery streams in this project. The results thus far are reported in Attachment V-1 while current research activities are outlined in V-2.

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6. SPS-7: Synfuels Toxicology

Under this project, the subchronic toxicity of raw and selected levels of hydrotreated shale oil will be characterized in 28-day rat dermal studies, (Attachment VI-1). A high nitrogen crude will also be tested for comparative purposes. The samples have been prepared and the task force has selected Springborn Research Institute to conduct the tests.

C. Reproduction/Teratology

The final report, on the xylene reproduction/teratology study has been accepted. The only treatment related effect was maternal toxicity at the 500 ppm level. The final report will be submitted under TSCA section 4.

The two generation inhalation reproduction/teratology study on toluene began October 31, 1984 at IRDC. The study design is essentially similar to a 1 generation study, except that it is extended to 2 generations. The exposure levels are 100, 500, and 2000 ppm. The study is being conducted in lieu of TSCA section 4 test rule. There have been some problems with the hourly IR readings for the control chamber--they are routinely in the low ppm range (1-10 ppm) with occasional peaks at 40 ppm. In order to verify chamber concentrations, the charcoal tube samples were obtained in the control chambers over a two week period, and analyzed by Clayton Environmental Consultants using a NIOSH approved method. This analysis showed that the toluene concentration in the control chamber was below the limit of detection, 0.009 ppm. Currently, charcoal tube samples are being taken in the exposure chambers over three days. Saul Blum has already visited IRDC to examine their analytical system, and he will also examine the daily IR measurements, the charcoal tube sampling, and other study data being obtained from IRDC. The Task Force will consider Dr. Blum's evaluation, and the charcoal tube data, when they decide whether or not to continue the study--this decision will be made prior to mating which is scheduled for January 18. API staff will brief HSRD on the status of the study in an effort to get guidance on possible EPA discussions.

Toluene-induced auditory effects have been reported in the literature. The Task Force plans to evaluate adding auditory studies to the protocol. P. Craig

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and several members of the Toxicology Committee strongly recommended that auditory studies be done but not in conjunction with the present toluene study.

The single generation reproduction study with hexane has been delayed until the toluene study is proceeding smoothly.

Planning for the gasoline reproduction study remains on hold while background information is obtained from the Industrial Hygiene Committee, Environmental Affairs Department's Groundwater Task Force (Ben Thomas is the liaison), PS-32 Skin Absorption, and the Occupational Health Committee. Leon Golberg will be asked to prepare a report on species selection. Dr. Kuna will request progress reports from the above groups at 2-month intervals. The study plan presentation to HESC is targeted for the third quarter.

D. Genetic Toxicology

1. Mutagenic Potential (PS-4)

C. Schreiner presented an update on the status of the refinery streams currently on test at Litton and Microbiological Associates. (Table VII.) Eight additional samples will be sent to the contractors in 1984. The work under PS-4 should be completed in 1984. The methods currently being validated in PS-12 will become part of the standard mutagenesis battery beginning in 1985.

2. Methods Development (PS-12)

Ames Assay modifications are being investigated at Microbiological Associates. The work to date has shown that increasing the concentration of rat S-9 and NADP yields an increased mutant response. Several PS-8 samples which had previously been negative, have now tested positive in the presence of higher concentrations of S-9 and NADP. (Refer to Table VIII.) The next set of studies includes the use of hamster S-9 activation, and Tween 80 emulsions.

C. Schreiner presented the Ames Assay Development work from her laboratory. (Tables IX-XII.) They have also used hamster S-9 at 8-fold concentration

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and 2X NADP to get increased mutant response. Mobil then computes the Mutation Index (slope of the initial portion of the dose-response curve) and a Carcinogenesis Index from skin painting results:

$$C.I. = \frac{1}{\text{Ave. latency}} \times \frac{\text{No. animals w/tumor}}{F E N}$$

$$\times \frac{1}{\log \text{ dose}} \times \frac{1}{\text{application frequency}} \times 10,000$$

Test materials are then ranked according to their M.I. and C.I. Dr. Schreiner presented graphs correlating the M.I. and C.I. rankings. For the middle and heavy distillates, the correlation is quite good, with the exception of the C-4 aromatics. Mobil uses an in-house 100 SUS oil as its positive control. Dr. Schreiner recommended that API establish a repository for reference materials to be used as positive controls across the industry.

Dr. Conaway reported that the final report on the liposome delivery system for cell transformation had been received last week. The major short coming of the work was improper experimental design--too many parameters were changed in each experiment. Due to limitations of time and money, these discrepancies were not corrected. The investigator, Dr. Landolph, USI, will submit a manuscript describing the work to a peer reviewed journal. The Task Force plans to pursue additional liposome/cell transformation studies when funds become available.

Validation of several assays is planned for 1984: 1) Sister Chromatid Exchange, 2) HGPRT mutation in CHO cells, and 3) Unscheduled DNA Synthesis. Cat cracked clarified oil, C-5 aromatics, and raw shale oil will be used in these validation studies. When the validation studies are completed, the three assays will become part of the standard mutagenesis battery for PS-4 positives.

2. Carcinogenesis

1. Carcinogenic Potential of Crude Oil and Distillates (PS-8)

The Task Force has accepted final reports for the Phase I (1976) and Phase II (1970) skin painting studies. Dr. Stemmer's monograph on historical controls has also been received. Dr. Lewis commented upon and thanked Rod Anderson, API QA staff, for his efforts in working with Kettering technical staff to improve the quality of their work, recordkeeping, and health and safety aspects of the work.

Oak Ridge National Laboratories are preparing Weibull curves on the PS-8 data. Oak Ridge is doing the work on a pro bono basis, so there is no rigid delivery data.

Initiation/Promotion Studies are now in their 70th week. These interpretations can be drawn: C-2 and D-2 naphthas are weak promoters, and cocarcinogens, and they may counteract the effects of TPA in un-initiated animals. C-2 and D-2 are not initiators. The Task Force decided to continue the I/P studies to their full 2 years in order to get the last ounce of value and information from the study.

Dr. Lewis plans to present the I/P study results at the International Skin Painting Symposium in France in June.

The chemical treatments project failed to receive approval from HESC. The Task Force reviewed four alternatives and decided to close out PS-8 with the end of the I/P studies, and to consider redesigning a chemical modifications proposal for consideration in 1985 under a new PS number. A final report on PS-8 will contain an administrative summary (critical dates of contracts, study start ups, and ending dates, reports received) and a technical summary.

Gulf requested and received PS-8 samples to be used as positive controls in their tox program. Gulf will periodically update API on the status of these samples.

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The Task Force had hoped to be able to correlate chemical composition and biological activity, and had planned on using the PS-24 report (Chemical Analysis of Heterocycles in Petroleum Crude Oil). However, this report indicates that heterocycle analysis is extremely difficult and a standardized methodology directly applicable to all oils was not developed. Some assistance for the chemical/biological relationship may be available in the soon-to-be-released CONCAWE document which included potency rankings for 90 petroleum hydrocarbon materials.

The effort to have Dr. John Weisburger prepare a monograph on the interpretation and extrapolation of PS-8 data to predict occupational skin hazards has been abandoned. The task force will now turn its attention to the proposal by Trump and Lipsky. Drs. Golberg and Sternberg will be asked to advise the Task Force on the merits of the Trump and Lipsky proposal.

2. Carcinogenic Potential of Refinery Streams - PS-36

The Task Force has accepted Kettering's final report of skin painting studies of paraffinic and naphthenic base stocks.

The Task Force has received a final report from Borriston Labs on the refinery streams skin painting study which had to be aborted due to a 95 percent incidence of mouse hepatitis virus.

The refinery streams study has been moved to the Primate Research Institute. A sentinel health screen lasting 4 weeks was conducted before the chronic animals were ordered. This health screen showed that Jackson Lab mice have endemic Pneumonia Virus of Mice but it disappears after 4 weeks at PRI. A prestudy conference held in November included a tour of the facilities and the new air handling system. The 1900 skin painting animals were quarantined over the Holidays. About 60 animals died between day 3-6 due to the stress of shipping from Maine to New Mexico. There has been no further mortality. The study will begin January 12, 1984. Rod Anderson, API QA, will conduct an audit after the 2nd week of the study.

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Additional refinery streams will be tested in 1984. There are currently 8 samples available. The Task Force wants to use at least 2 different laboratories for its projects and to have the projects operating concurrently. Bushy Run and Hazleton were suggested by the Toxicology Committee members for laboratories for the next set of studies.

3. Carcinogenic Potential of Hydrotreated Shale Oil and Distillates - SYN-8

Dr. Lewis reported for Dr. Nees. The test samples for this skin painting study are: a raw shale oil and 2 hydrotreated shale oils produced from it, a second raw shale oil and its daughter hydrotreated shale oil, and a high nitrogen crude petroleum. Distillate fractions similar to those in PS-8 are being prepared now and should be available in mid-February. Battelle Northwest Labs was chosen as the laboratory with Roger Renne as the principal investigator. A prestudy conference will be held prior to the initiation of the pilot study. In the pilot study, 2 distillates each from the 5 whole oils will be painted at doses of 3X25 mg and 3X10 per week for 4 weeks. Battelle will be using the C3H mouse from Charles River because the Charles River mice are free of lung pathogens which are present in Jackson mice. Battelle is currently free of endemic pathogens and did not want any imported. Although the Charles River C3H mouse is a different substrain of C3H mouse than the Jackson mouse, no impact on study results and evaluation is anticipated.

IV. OTHER BUSINESS

Suggestions for the summer meeting date and location were requested. Dr. Lewis reminded the committee that the International Skin Painting Symposium is scheduled for June 19-22 and that the Toxicology Forum is scheduled for the week of July 16. The summer meeting was therefore tentatively scheduled for the 1st full week in July after the July 4th holiday. Washington, D.C., Denver, and Phoenix were suggested as sites.

V. CLOSING REMARKS AND ADJOURNMENT

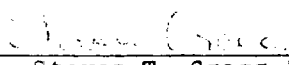
Dr. MacGregor thanked API staff for their efforts in planning and conducting the meetings during the last few days. The quality and extent of discussions and decision-making at the Task Force and full committee meetings were very high.

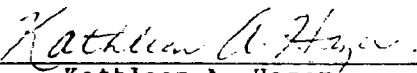
The meeting adjourned about 3:00 p.m.

Submitted by:


J.A. MacGregor
Chairman
Toxicology Committee

Prepared by:


Steven T. Cragg
API Staff


Kathleen A. Hazer
API Staff

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Program Status on MTBE

MTBE, methyl-t-butyl ether, is being manufactured for use as an octane enhancer in motor fuels by a number of companies. A program of toxicological evaluation of MTBE was begun in 1980 by a group of six American companies and one German producer under the auspices of the API. The program consists of a 9-day inhalation toxicity study, a two-species teratology study and a single-generation reproduction/fertility study also by inhalation, and a pharmacokinetics-metabolism study. A 90-day subchronic inhalation toxicity study was done by the German producer earlier, in which essentially no adverse studies were also performed independently by participating companies.

A report of the 9-day inhalation probe has been received from Bio/dynamics. Exposures were 0, 100, 300, and 3000 ppm. A reduced response to auditory stimuli and lassitude was observed in the rats exposed to 3000 ppm, indicating some central nervous system depression. Liver weights, both absolute and relative, were also observed, but there were no definitive histopathological changes. The no effect level was determined to be above 300 ppm.

Exposures for the two-species teratology study were completed in September 1981. A single generation reproduction study was completed in early 1982. No significant effects were observed on fertility, fetal development, or pup survival. MTBE is therefore not considered maternally toxic, embryotoxic, or teratogenic. The actual test exposures in these studies were approximately 300 ppm, 1200 ppm, and 3000 ppm, and are 20 percent above the target concentrations. Bio/dynamics, the contractor, reported some experimental errors that caused these excursions. The audit of the teratology and reproduction reports by Tracor Jitco, the quality assurance contractor, and by API revealed some inconsistencies which will be corrected in the final report.

The pharmacokinetics work shows that elimination of MTBE is apparently biphasic, with plasma elimination half lives of 7 hours and 23 hours, respectively. The major route of elimination of an i.p. dose is by expiration; from 70 to 90 percent of the applied dose was trapped in toluene bubblers. Less than 10 percent of the dose was detected as $^{14}\text{CO}_2$, indicating a relatively small degree of metabolism. Less than 5 percent is excreted in urine and feces. The highest amounts of tissue radioactivity were in the liver and kidneys. Metabolite identification and quantification was performed on plasma, kidney, and liver tissues. Formic acid was the major metabolite in pooled urine and feces samples.

A final report of all work performed at Bio/Dynamics is anticipated by March 1, 1984. No additional testing or research is planned at this time.