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RESEARCH PROGRAM PROGRESS REPORTS

Health and Environmental Sciences Department

February 1989

Editor: Judith G. Shaw
Editorial Assistant: Elsie Barbaza

American Petroleum Institute
1220 L Street, Northwest
Washington, DC 20005

have had relatively high exposure to gasoline vapors. The work includes the integration of two segments: 1) an epidemiology study ascertaining the work histories and mortality and 2) an exposure assessment study characterizing exposures.

Status: Epidemiology: the contractor has coded the employment histories of approximately 80 percent of the employees estimated to be members of the final cohort. The contractor is also performing estimations of error rates in the coding process. The task force and contractor are investigating various means of providing independent estimates of cohort verification.

Exposure Assessment: Industrial hygiene (IH) surveys at older distribution and marketing facilities have been completed. An IH workshop was held in November 1988 and a follow-up is planned for April, 1989, to finalize the historical data characterization and plan for the integration of the IH and epidemiological data.

Anticipated Completion Date: December 1989

LIGHT HYDROCARBON-INDUCED NEPHROTOXICITY – PS-67

Staff: E.H. Vernot

Objective: To elucidate the mechanisms of light hydrocarbon-induced nephrotoxicity and carcinogenicity.

Initiated: 1983; $1,750K; Contractor: Chemical Industry Institute of Toxicology (CIIT)

Scope: With the identification of the compound types responsible for male rat nephropathy, mechanistic studies were undertaken to determine the pathogenesis of male rat kidney lesions. These included binding studies with a nephrotoxic metabolite and a male rat specific serum protein (alpha-2u-globulin), cell proliferation in the kidneys of exposed male rats, initiation/promotion experiments, and a search for human serum proteins related to alpha-2u-globulin.

Status: Studies have indicated that a cascade of events must occur for the kidney tumors to occur: strong binding between the chemical and the protein, accumulation of the protein in lysosomes to the point where the lysosomes rupture leading to cell toxicity and death, and increased cellular proliferation which acts as a promoter to increase the rate of background tumors. More recent studies are focusing on the characteristics of human proteins related to alpha-2u-globulin. Exposure of male rats to European high test gasoline did not produce the nephrotoxic effects associated with PS-6 gasoline. The European product contains only small amounts of the isoparaffins believed responsible for the kidney toxicity and carcinogenicity. CIIT has published many papers on this work in the scientific literature.

Anticipated Completion Date: December 1989

SOURCE APPORTIONMENT OF BENZENE IN HUMAN BREATH AND AMBIENT AIR BY 14C ANALYSIS

Staff: W.M. Ollison

Objective: To develop a methodology to sample and separate trace benzene in air and breath and assay 14C to distinguish fossil fuel sources of benzene from other sources.

Initiated: May 3, 1988; $55K; Grantees: Drs. L. Currie and S. Wise, National Institute of Standards and Technology (formerly National Bureau of Standards).

Scope: The procedure will concentrate trace benzene from air/breath on absorber columns, elute and separate benzene by supercritical fluid chromatography and assay 14C by accelerator mass spectroscopy. Task 1 will develop the separation methodology; Task 2 will validate this methodology with standard samples and Task 3 will test this methodology in ambient settings.

Status: Initial progress report for Task 1 received October 27, 1988. Draft report expected August 1989

Anticipated Completion Date: October 1989

BENZENE IN NUTRIMENTS – PS-72

Staff: E.H. Vernot

Objective: To estimate the contribution of the average American diet to the total body burden of benzene by analyzing important foods and be

Initiated: 1988; $45K; Contractor: The National Food Lab

Scope: An initial list has been drawn up for analysis incl ; and vegetables, 3 beverages, and eggs. All vegetables will b ınd selected items will be cooked. The eggs will be tested raw, boiled and fr list has also been formulated which includes meats, dairy products, a ucts. These will be analyzed following the first series.

Status: Work began in February 1989.

Anticipated Completion Date: March 1990

CHRONIC BENZENE TOXICOLOGY - PS-7B

Staff: E.H. Vernot

Initiated: 1986; $22K; Contractor: Bio/dynamics

MCD 000015039

Objective: To determine the feasibility of delivering benzene to rodents in drinking water.

Scope: Mice were exposed for 2 weeks to benzene in drinking water at concentrations ranging from 100 mg/l to 700 mg/l. Stability of benzene in the water bottles and water consumption will be measured.

Status: Report in preparation.

Anticipated Completion Date: 2nd Quarter 1989

MECHANISMS OF BENZENE TOXICITY – PS-65

Staff: E.H. Vernot

Objective: To expand our understanding of the mechanisms of benzene toxicity (leukemogenesis, hematotoxicity, and in rodents) so that the relevance of such observations to human health can be assessed; to understand the quantitative and qualitative relationships between benzene exposure and leukemia; and to explore means to biologically monitor benzene exposure in humans.

Initiated: 1986; $250K; Contractor: CIIT

Scope: Initial studies will characterize the genesis of mouse leukemias to compare potential mechanisms of leukemogenesis between mice and humans. Researchers will then attempt to develop model culture systems for comparing the relative sensitivities and mechanisms of hematopoietic and lymphoid injury in mouse and human cells. Further efforts to validate or implement biological monitors of benzene exposure identified in these studies may be the subject of future proposals.

Status: In a preliminary experiment myelogenous leukemia has developed in C57BL/6 mice after 12 weeks of intermittent exposure to 100 or 300 ppm benzene. A bioassay to confirm these results has been completed and is being analyzed. A group of CBA/Ca mice, which are not subject to virally induced leukemia, is being exposed chronically.

Anticipated Completion Date: 1993

BENZENE PHARMACOKINETICS AND RISK MODELING - PS-66

Staff: E.H. Vernot

Objective: To develop a physiological pharmacokinetic model of benzene intake, distribution, and elimination that reproduces experimental data in animal and human models. This is the first step in establishing a risk assessment model based on known biological processes rather than theoretical constructs.

Initiated: 1988; $88K; Contractor: Martin Marietta (Oak Ridge National Laboratory)

Scope: Using accepted pharmacological constants and adjusting metabolic parameters, benzene concentrations in blood, breath, and tissues, and total body burden of benzene are accessible from the model. These closely simulate the data obtained from experiments on rats, mice, and humans. Successful simulations of ambient or near-ambient exposures have been achieved by incorporating low-level benzene binding in the blood. Future efforts will investigate the binding of benzene in the blood and incorporate cellular growth kinetics into a benzene risk model.

Status: Reports have been received detailing the pharmacokinetic model and the rationale for benzene binding in the blood.

Anticipated Completion Date: November 1989