702 COMPARATIVE EFFECTS OF QUINOLINE AND 8-HYDROXYQUINOLINE ON GLUTATHIONE LEVELS, DNA FRAGMENTATION AND ENZYME INDUCTION IN CULTURED RAT HEPATOCYTES. M A Tirmenstein, J E Snawder, P I Plews and M Torasson. Cellular Toxicology Section, ETB, DBBS, NIOSH, CDC. Taft Laboratories, Cincinnati, OH.

Quinoline and 8-hydroxyquinoline (8-HQ) are major industrial chemicals. Quinoline is also a constituent of automobile exhaust, tobacco smoke and indoor air pollution. Studies have shown that quinoline is a hepatocarcinogen and potent mitogen in rats and mice. 8-HQ, however, failed to induce hepatic carcinogenesis when tested in rodent chronic bioassays, and is not known to produce a mitogenic response in rat liver. The following study was conducted to assess the comparative effects of quinoline and 8-HQ on hepatocyte function. Exposure to quinoline for 3 hrs depleted hepatocyte glutathione (GSH) levels in a dose-dependent manner. The addition of 500 μM quinoline depleted GSH levels to about 60% of control values after 3 hrs. Quinoline did not induce the formation of oxidized glutathione (GSSG) at the concentrations tested. Exposure to 500 μM 8-HQ for 3 hrs also depleted hepatocyte GSH to about 70% of control values, but GSH loss could be accounted for by increases in GSSG levels. Lower concentrations of 8-HQ did not deplete glutathione levels at the 3 hr timepoint. Both compounds induced increases in single-strand DNA breaks at selected concentrations as judged by alkaline elution analysis, but 8-HQ induced increases in DNA single-strand breaks were associated with cytotoxic concentrations of 8-HQ. Hepatocytes cultured for 48 hrs and subsequently exposed to quinoline or 8-HQ exhibited increased levels of ornithine decarboxylase activity 4 hrs after the addition of the chemicals. The result of this study suggests that quinoline and 8-hydroxyquinoline have significantly different effects on hepatocyte function.

703 INHIBITION OF FERROCHELATASE AND INDUCTION OF PROTOPORHYRIA IN CULTURED DOG HEPATOCYTES BY DAPOXETINE. PS Foxworthy, DN Perry, KI MacKenzie, PI Eacho. Toxicology Research Laboratories, Eli Lilly and Company, Greenfield, IN

Dapoxetine (DPX) is a 5-HT re-uptake inhibitor developed for the treatment of depression. In subchronic studies in dogs DPX increased hepatic and blood protoporphyin levels. The compound was not porphyrinogenic in rats. To facilitate studies of the mechanism of DPX porphyria, an in vitro model was developed using rat and dog hepatocytes. Cells were cultured in L-15 media in the presence or absence of aminolevulinic acid (ALA). DPX was dissolved in DMSO and added 4 hr post-seeding and every 24 hr thereafter. The addition of ALA to the media increased cell and media porphyrins in dog hepatocytes approximately 8-fold. DPX alone did not increase cell or media porphyrins. In the presence of ALA, DPX increased cell porphyrin levels 4-fold above those acheived by ALA alone. The cellular porphyria was predominatly protoporphyrin IX, which is consistent with the in vivo data. This was associated with a dose-related inhibition of ferrochelatase activity (maximum inhibition 88%). In rat hepatocytes DPX had no effect on porphyrin levels or ferrochelatase activity. In contrast, rat hepatocytes did respond to the porphyrinogenic agent ethyl 3,5-diethoxycarbonyl-1,4-dihydrocollidine. The data indicate that the dog and rat hepatocytes accurately model the porphyrinogenic response to DPX. These models will facilitate studies of the metabolism of DPX and other factors which may be involved in the interspecies differences in the porphyrinogenic response.

704 *IN VIVO* AND *IN VITRO* ASSESSMENTS OF PF10,040 HCL ON RAT HEPATIC ENZYME INDUCTION. L Buchanan[1], N Galarneau[1], L Huard[1], G Huard[1], G Duguay[1] and J Tigner[2]. [1]Bio-Research Laboratories Ltd., Quebec, Canada and [2]Purdue Frederick Research Center, Yonkers, NY.

PF10,040 HCl is a novel leukotriene- and PAF-inhibitor. Toxicological studies with PF10,040 HCl in rats showed dose-dependent increases in liver weight after 14 days of treatment with 200, 400 and 600 mg/kg p.o. In the present study, hepatic enzyme induction was assessed in male and female Sprague Dawley rats pre-treated p.o. for 3 consecutive days with 25, 100 and 400 mg/kg of PF10,040 HCl. Control animals received 3 consecutive daily oral doses of distilled water, or i.p. injections of phenobarbital, β-naphthoflavone or the appropriate vehicle (saline, corn oil). On Day 4, hepatic induction was assessed (1) *in vivo*, by monitoring the duration of zoxazolamine paralysis or hexobarbital sleeping times and (2) *in vitro*, by determining the activities of hepatic microsomal cytochrome P450 mixed function oxidase and glucuronyl transferase enzymes. PF10,040 HCl (400 mg/kg) significantly reduced hexobarbital sleeping time in females *in vivo*, and increased the enzymic activities of 7-ethoxyresorufin O-deethylase (EROD) in both sexes and 7-ethoxycoumarin O-deethylase (ECOD) in females. Thus the high dose of PF10,040 HCl appeared to be a relatively weak hepatic enzyme inducer, particularly in female rats.

705 HEPATIC CYTOCHROME P450 INDUCTION IN DOGS AND RATS BY THE CYCLOOXYGENASE AND 5-LIPOXYGENASE INHIBITOR CI-1004. L M King, R J Guttendorf, B J Houston, D W Clarke and R M Walker. Parke-Davis Research Institute, Mississauga, ON.

CI-1004 (Z)-(5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2-imino-4-thiazolidinone, methanesulfonate) has potent anti-inflammatory activity in animals. Hepatic cytochrome P450, enzyme activities (ethoxy-[EROD], pentoxy-resorufin O-dealkylase [PROD] and erythromycin N-demethylase [ERY]) and CI-1004 plasma concentrations were determined in 2-week oral studies in Wistar rats and beagle dogs. Total P450 was elevated in male rats at 35-250 mg/kg and female rats at 75 and 100 mg/kg. In dogs, total P450 was doubled at 10 mg/kg and was higher than controls at 5 mg/kg in males and at 2 and 5 mg/kg in females. Western blotting with anti-rat cytochrome P450 IIB1/2 or IIIA antibodies showed increased amounts of these isozymes in rats and dogs. The results of the enzymatic assays supported induction of P450 IIB1/2 and IIIA. Compared to controls, PROD increased in both sexes of rats at 35-250 mg/kg, in female dogs at 2-10 mg/kg and in male dogs at 5 and 10 mg/kg. ERY was increased in dogs at 5 and 10 mg/kg and in male rats at all doses. Plasma concentrations indicated that CI-1004 metabolism is not altered by induction. In summary, CI-1004 causes dose-dependent induction of hepatic cytochrome P450 IIB1/2 and IIIA in dogs and rats which did not affect its own metabolism.

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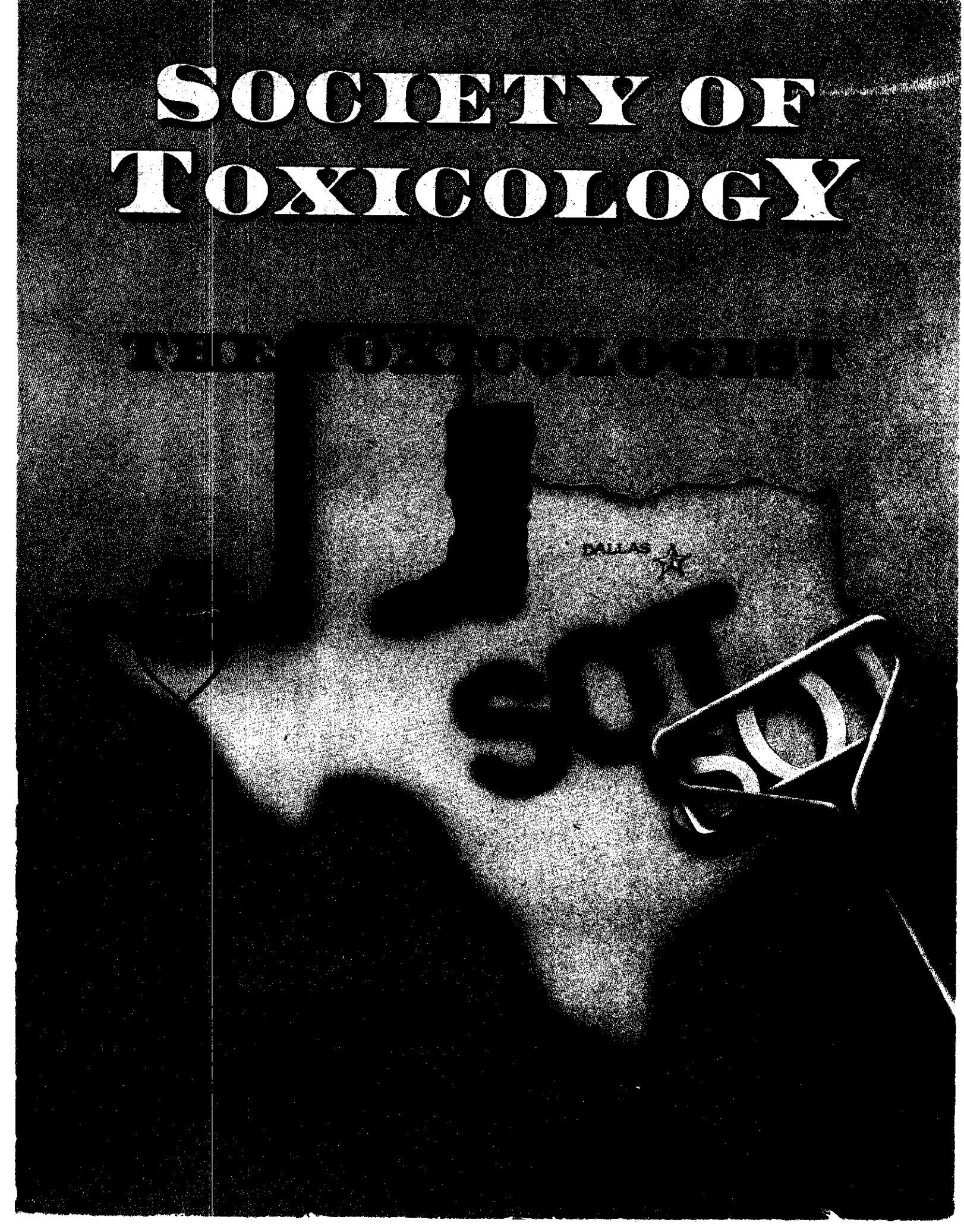

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Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the symposium, platform, poster/discussion, and poster sessions of the 33rd Annual Meeting of the Society of Toxicology, held at the Loews Anatole Hotel, Dallas, Texas, March 13-17, 1994.

An alphabetical Author Index, cross-referencing the corresponding abstract number(s), begins on page 439.

The issue also contains a Keyword Index (by subject or chemical) to the titles of all the presentations, beginning on page 467.

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