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211 (b) Research Group

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1201 Pennsylvania Ave., NW
Washington, DC 20460-0001

Re: TSCA (8e) Submission for Clean Air Act Section 211(b) Gasoline/Ethanol Vapor
Condensate (Lot # API 01-03)

Dear Sir/Madam:

The 211(b) Research Group (see attached membership list) is an unincorporated group of US fuel and fuel additive manufacturers affiliated by contractual obligation to meet the testing requirements of Section 211(b)(2) and 211(e) of the Clean Air Act. The 211(b) Research Group, on behalf of its member companies, is submitting this notice pursuant to TSCA Section 8(e). This notice is based on preliminary results from one of the required studies, an assay in rats to evaluate potential neurotoxicity by measuring glial fibrillary acidic protein (GFAP) concentrations in the brain after inhalation exposure to gasoline/ethanol vapor condensate. The study found statistically significantly increased GFAP levels in brains of male rats exposed to gasoline/ethanol vapor condensate by inhalation for 13 weeks.

The significance of these GFAP results for human health hazard assessment is unknown at this time. To our knowledge, the regulatory and industry communities do not have a great deal of experience in interpreting the GFAP assay results for use in human health hazard assessment. Nevertheless, the Research Group wishes to err on the side of caution and submit the data under Section 8(e).

As part of the 211(b) Alternative Tier II test program on gasoline (CAS No. 86290-81-5) containing 10% ethanol (CAS No. 64-17-5), the GFAP assay was performed on tissue from nine areas of brain from rats (5/sex/group) exposed to gasoline/ethanol vapor (13% ethanol) by inhalation at concentrations of 0, 2,000, 10,000 and 20,000 mg/m³, 6 hr/day, 5 days/week for 13 weeks. After the final exposure, animals were sacrificed, brains removed, and freehand sections of brain areas made. Individual tissue samples were homogenized in SDS, and GFAP levels were measured by Sandwich ELISA. Unaudited

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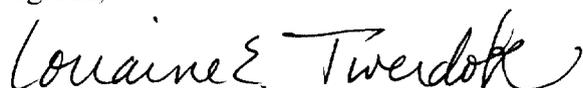
data underwent analysis of variance followed by post-hoc comparison of treatment means, using a significance level of $p < 0.05$ (summary table attached). Exposure to the gasoline ethanol vapor condensate caused slight increases in GFAP in several brain regions in males. In general, these increases were not concentration-related. However, GFAP in cerebellum was statistically significantly increased at all exposure concentrations. The degree of GFAP increase (approximately 30%) was marginal, indicating minor gliosis. No signs of neurotoxicity were observed in these animals before sacrifice (ie, in the FOB and tests of motor activity), and no neuropathological findings were evident. Statistically significant increases in GFAP were not detected in females.

Preliminary results from a similar study with unoxygenated gasoline vapor in rats were negative in both sexes. Additionally, GFAP findings have been reported in rats administered ethanol alone via the oral route¹.

In rats, increased levels of GFAP are interpreted as very early markers of potential neurotoxicity. However, even in rats it is difficult to extrapolate increases in GFAP to overt neurotoxicity due to the many redundant neural pathways of the brain.

When the final report of the GFAP Assay study is complete, it will be submitted to the EPA Office of Transportation and Air Quality, Fuels and Energy Division, as part of the requirements of Clean Air Act Section 211(b)(2) and 211(e) (Docket No. A-90-07). If you require further information, please contact Lorraine Twerdok at 202-682-8344, or by mail at this address.

Regards,



Lorraine Twerdok, Ph.D., DABT
211(b) Research Group Program Administrator

Cc: John Brophy, EPA
Mike Davis, EPA
Monica Alvarez, EPA
Tom Goldsworthy, ILS
Rich Schlesinger, NYU
211(b) Research Group Member Companies

¹ Franke, H. et al. The reaction of astrocytes and neurons in the hippocampus of adult rats during chronic ethanol treatment and correlations to behavioral impairments. *Alcohol*, 1997, 14(5):445-54.

Table 5: Mean GFAP Levels in Specific Regions of Male Rat Brains Following a 13 Week Whole-Body Inhalation Exposure to Gasoline ETOH Vapor Condensate

Brain Area	Group I Air Control 0 mg/m ³	Group II Test Substance 2,000 mg/m ³	Group III Test Substance 10,000 mg/m ³	Group IV Test Substance 20,000 mg/m ³
Striatum	0.94 ± 0.10*	1.28 ± 0.18	1.44 ± 0.29*	1.10 ± 0.14
Hippocampus	2.91 ± 0.15	3.46 ± 0.39	3.40 ± 0.31	2.91 ± 0.14
Cortex	1.06 ± 0.07	1.40 ± 0.12*	1.33 ± 0.12	1.18 ± 0.08
Olfactory Bulb	2.28 ± 0.13	3.03 ± 0.36*	2.88 ± 0.15	2.48 ± 0.22
Thalamus	1.53 ± 0.09	2.30 ± 0.18*	1.97 ± 0.30*	1.73 ± 0.14
Hypothalamus	7.52 ± 1.03	8.53 ± 0.26	7.34 ± 0.78	7.44 ± 1.09
Cerebellum	3.49 ± 0.14	4.52 ± 0.25*	4.62 ± 0.36*	4.42 ± 0.32*
Pituitary	0.05 ± 0.00	0.07 ± 0.00	0.07 ± 0.00	0.06 ± 0.00
Rest of Brain	3.53 ± 0.27	4.54 ± 0.51*	3.92 ± 0.19	3.89 ± 0.32

*Each value represents the mean ± SEM (Standard Error of Mean) for the concentration of GFAP (µg/mg Total Protein)

n= 5 except for Pituitary; see Results and Conclusion and Table 7

*Statistically different from Air Control, P< 0.05

Table 6: Mean GFAP Levels in Specific Regions of Female Rat Brains Following a 13 Week Whole-Body Inhalation Exposure to Gasoline ETOH Vapor Condensate

Brain Area	Group I Air Control 0 mg/m ³	Group II Test Substance 2,000 mg/m ³	Group III Test Substance 10,000 mg/m ³	Group IV Test Substance 20,000 mg/m ³
Striatum	0.94 ± 0.12*	1.24 ± 0.19	1.00 ± 0.09	1.04 ± 0.14
Hippocampus	2.76 ± 0.13	3.13 ± 0.13	2.91 ± 0.21	2.90 ± 0.21
Cortex	1.10 ± 0.06	1.26 ± 0.15	1.13 ± 0.08	1.16 ± 0.10
Olfactory Bulb	2.57 ± 0.15	3.15 ± 0.31	2.53 ± 0.26	2.96 ± 0.19
Thalamus	1.54 ± 0.09	1.61 ± 0.14	1.73 ± 0.14	1.57 ± 0.06
Hypothalamus	7.34 ± 0.73	8.21 ± 1.03	9.62 ± 1.05	8.48 ± 0.44
Cerebellum	3.65 ± 0.15	3.93 ± 0.22	4.17 ± 0.34	3.97 ± 0.41
Pituitary	ND	ND	ND	ND
Rest of Brain	3.65 ± 0.13	3.92 ± 0.44	3.92 ± 0.29	3.91 ± 0.31

*Each value represents the mean ± SEM for the concentration of GFAP (µg/mg Total Protein)

n= 5; ND, not detected

SECTION 211(b) RESEARCH GROUP MEMBERSHIP YEAR 2002

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