Health Consultation

Exposure Investigation

Biological and Environmental Monitoring for Exposure to Benzene and Related Petroleum Chemicals

CORPUS CHRISTI, TEXAS

Cost Recovery Number: A835

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry
Division of Health Assessment and Consultation
Atlanta, Georgia 30333

Health Consultation: A Note of Explanation

An ATSDR health consultation is a verbal or written response from ATSDR to a specific request for information about health risks related to a specific site, a chemical release, or the presence of hazardous material. In order to prevent or mitigate exposures, a consultation may lead to specific actions, such as restricting use of or replacing water supplies; intensifying environmental sampling; restricting site access; or removing the contaminated material.

In addition, consultations may recommend additional public health actions, such as conducting health surveillance activities to evaluate exposure or trends in adverse health outcomes; conducting biological indicators of exposure studies to assess exposure; and providing health education for health care providers and community members. This concludes the health consultation process for this site, unless additional information is obtained by ATSDR which, in the Agency's opinion, indicates a need to revise or append the conclusions previously issued.

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Executive Summary

The communities of Hillcrest and Dona Park are located near "refinery row," a large complex of petroleum refineries in Corpus Christi, Texas. Residents of these communities have expressed concern over possible exposures to benzene and other volatile organic compounds (VOCs) in petroleum products that may be emitted from the refineries.

To address these concerns, ATSDR conducted an exposure investigation (EI). ATSDR worked with community representatives to recruit residents who lived near the refineries. ATSDR visited 90 residents in their homes and collected personal air, blood, and urine samples, which were tested for benzene and related petroleum VOCs.

The concentrations of benzene and other petroleum-related VOCs detected in personal air samples from the EI participants were not higher than those detected in residents of the United States in a national survey (NHANES).

There was no evidence of widespread exposure to elevated concentrations of environmental VOCs. Elevated concentrations of VOCs detected in a few personal air samples were possibly due to direct contact with fuels or other consumer products containing petroleum solvents.

The concentrations of benzene and other petroleum-related VOCs detected in blood samples from the EI participants were not higher than those detected in residents of the United States in a national survey (NHANES).

Tobacco smoking is a significant source of exposure to VOCs, and the EI participants who smoked had higher VOC exposures than non-smokers.

The conclusions of this health consultation are based on the time period during which this exposure investigation was conducted. This report draws no conclusions regarding past or future exposures to VOCs in the community. ATSDR is currently preparing a public health assessment that will examine the health impact of long-term and short-term exposures to benzene and other air contaminants.

Introduction

From October 2007 to March 2008, researchers from Texas A&M University (TAMU) collected blood and urine samples from residents living near "refinery row" in Corpus Christi, Texas. The stated purpose of this pilot project was to "develop appropriate protocols for biomarkers of exposure to petroleum hydrocarbons." This project was a collaborative effort of the Citizens for Environmental Justice (CFEJ), TAMU School of Rural Public Health, and the Coastal Bend Health Education Center (CBHEC).

TAMU reported that benzene concentrations in many of the blood samples were elevated. Some of the reported benzene concentrations (up to 542 nanograms/milliliter) were more than 1,000-times higher than the 95th percentile of the blood benzene concentrations from the National Health and Nutrition Examination Survey (CFEJ-TAMU-CBHEC, 2010).

When analyzing blood samples for volatile organic compounds (VOCs), it is important to prevent contamination of the samples with external VOCs during the collection and processing of blood samples. For example, rubber stoppers in blood collection tubes contain residual VOCs that must be removed by implementing procedures such as heating the stoppers in an oven for 21 days under a vacuum (Chambers et al. 2006). Other potential sources of bias include VOC contamination of laboratory air, water, or other materials. The failure to eliminate such sources of contamination can result in erroneously high results. The TAMU laboratory did not use a validated analytical method and did not provide quality assurance/quality control data, so it is not known if potential sources of contamination contributed to the findings of the study.

The TAMU test results, if accurate, would indicate that residents of the Hillcrest community were being exposed to large doses of benzene. ATSDR concluded that further investigation was warranted to determine if current exposures to benzene are elevated in residents living near refinery row.

Project Overview

Purpose

ATSDR conducted biological monitoring and environmental monitoring for exposure to benzene and related aromatic hydrocarbons in residents living near refinery row. This biological and environmental monitoring was conducted using validated, state-of-the-science analytical methodologies. The purpose of this investigation was to measure current levels of exposure to benzene and related petroleum VOCs using personal air, blood, and urine samples collected from residents who live near refinery row.

Investigators and Collaborators

The Agency for Toxic Substance and Disease Registry (ATSDR), Division of Health Assessment and Consultation (DHAC), Exposure Investigations and Site Assessment Branch (EISAB) was the lead for this exposure investigation (EI). EISAB collaborated with the

National Center for Environmental Health (NCEH/CDC) and the communities of Dona Park and Hillcrest to conduct this investigation. The roles of each are listed below.

EISAB:

(1) Worked with the community to recruit participants for the EI

(2) Procured passive air samplers for personal air monitoring

(3) Contracted for local phlebotomists to draw blood samples

(4) Administered consent/assent forms and questionnaires

(5) Collected environmental and biological samples and shipped them to laboratories for analysis

(6) Evaluated the analytical test results

(7) Notified the participants of their individual test results

(8) Served as primary authors of the final report

National Center for Environmental Health (NCEH):

(1) Provided supplies for collecting blood, urine, and water samples

(2) Analyzed blood, urine, and water samples for the chemicals of concern or their metabolites

(3) Interpreted analytical results and provided comparison data set

(4) Served as co-authors of the final report

The community:

(1) Provided input on selection of EI participants

(2) Assisted ATSDR in identifying and recruiting participants for the EI

Methods

Criteria for Participation

ATSDR worked with the community to recruit residents with the highest potential exposures to benzene and related aromatic hydrocarbons from refinery row. Participation in this EI was limited to people who lived in the communities of Hillcrest or Dona Park, which are contiguous to refinery row. Residents of these communities could potentially be exposed to contaminants from stack releases and flares, fugitive air emissions from the refineries, as well as to soil vapor intrusion from contaminated groundwater. The focus of the EI was on residents who live near refinery row, and who spend much of their time at home in their community. Thus, the participants of this EI were a biased sample whose exposures could be higher than the community-at-large. Although adults were the focus of this EI, children were also eligible to participate, as requested by the community.

Tobacco smoking is a significant source of exposure to benzene and other VOCs. Exposure to environmental tobacco smoke (second hand smoke) can be a lesser source of exposure to VOCs. Participants were questioned about their smoking habits, but smokers and their family members were not excluded from this EI. Participants from the previous TAMU study were also eligible to participate in the EI.

Recruiting Participants

ATSDR staff worked with the community to identify and recruit participants for this EI. Recruitment efforts included:

(1) ATSDR met with community leaders to discuss the proposed EI and solicit community input and support in contacting potential participants.

(2) ATSDR developed a fact sheet for distribution to the public that described the EI. The fact sheet included a toll-free number that participants could call to schedule an appointment for testing (Appendix A).

(3) Two-person teams consisting of one community member and one ATSDR staff person went door-to-door in Hillcrest and Dona Park to recruit participants for the EI.

Field Activities

In the TAMU pilot project, the participants drove to a local health clinic where blood samples were collected. Driving in a vehicle on a roadway is known to be a source of exposure to benzene in fuel and vehicular exhaust. Therefore, for this EI, ATSDR collected blood samples from people in their homes. Benzene concentrations in blood samples collected from people in their homes would be more indicative of what people are exposed to from ambient air in their neighborhoods and inside their homes. Furthermore, by collecting blood samples in people's homes, we were able to include participants who would not be able to travel to a different sampling location.

In order to maximize efficiency in collecting samples, ATSDR gave preference to households in which two or more people participated in the testing.

During the home visits, ATSDR conducted the following activities:

First Visit:

- Administered consent/assent form
- Distributed passive air samplers and explained how to use them
- Distributed urine collection cups and explained how to collect the sample
- Administered questionnaire

Second Visit (48 hours later):

- Collected exposed passive air samplers
- Collected urine samples
- Collected blood samples
- Collected tap water samples
- Completed questionnaire

Questionnaire

During the first home visit, ATSDR began to administer a questionnaire. The questionnaire solicited contact and demographic information from the participants and also included questions to assess potential exposures to VOCs from daily activities. During the second home visit, ATSDR asked additional questions that related to activities during the previous two days.

Environmental Testing

Personal Air

ATSDR gave the participants a passive air sampling device (3M^{TM} Organic Vapor Monitor 3500) for measuring VOC contaminants in the participant's personal air space. It has been demonstrated that these devices are effective in measuring low ($\mu g/m^3$) concentrations of benzene and other volatile organic chemicals in air (Begerow et al. 1999, Chung et al. 1999). A passive air sampler measures an individual's integrated exposure to VOCs over the time period of the EI, including both indoor and outdoor air.

The participants were instructed to attach the device to their shirt collar and wear it throughout the day at all times. At night, they were instructed to place it on a night table or other location near their bed. In the bathroom, they were instructed to place it in an area where it would not get wet by splashing water. The passive sampling device was worn for about 48 hours prior to collecting a blood sample.

Water

ATSDR collected tap water samples from 12 homes – 6 in Hillcrest and 6 in Dona Park. The faucet was run for 2 minutes to purge the supply pipe, the water flow was then reduced to a slow trickle to avoid aeration, and the water sample was collected into a screw-top, Teflon-lined vial.

The sample vial was filled until the water meniscus bulged over the top of the vial in order to avoid any air head-space in the vial. The water samples were stored at refrigerator temperature.

Biological Testing

Urine

ATSDR gave each participant a urine collection cup. The participant was instructed to collect a first-morning void or a random, spot urine sample of at least 30 milliliters (ml) on the day of ATSDR's second visit. After collecting the urine sample, the participant was instructed to cap the cup, seal it in a zip-lock bag provided by ATSDR, and place it in their refrigerator until collected. ATSDR retrieved the urine samples within 8-hours of collection, transferred a 5-ml aliquot of the urine into a cryovial, and froze it on dry ice. ATSDR transferred a second 2-ml aliquot of urine for creatinine analysis to a cryovial and froze it on dry ice. The urine samples were kept frozen and shipped on dry ice.

Blood

A phlebotomist collected a 10-ml blood sample in tubes that were specially prepared by NCEH for VOC analyses (Chambers et al. 2008). After collection, ATSDR kept the blood samples at refrigerator temperature (4° C) and shipped them on ice packs.

Sample Handling and Shipping

After collection, ATSDR stored the blood and water samples chilled and urine samples frozen. After all samples had been collected, ATSDR packaged the blood and water samples on ice packs and the urine samples on dry ice and shipped them by overnight delivery to the NCEH laboratory in Atlanta, Georgia, for analysis. All biological samples were shipped within 36 hours after collection.

ATSDR placed the passive air samplers in sealed canisters and shipped them at ambient temperature by overnight delivery to a contract laboratory for analyses (Bureau Veritas North America, Inc.; Novi, Michigan).

Lab Processing and Analysis

The blood, urine, and water samples were analyzed using published methodologies (Chambers et al. 2008; Ding et al. 2009) by the NCEH laboratory.

Blood samples were analyzed for the following chemicals:

Benzene
Toluene
Ethylbenzene
ortho-Xylene
meta- and para-Xylene
Methyl t-butyl ether (MTBE)

2, 5-Dimethylfuran (2,5-DMF)

Collectively, benzene, toluene, ethylbenzene, *o*-xylene, and *m&p*-xylene are known as BTEX.

Water samples were analyzed for the following chemicals:

Benzene
Toluene
Ethylbenzene
ortho-Xylene
meta- and para-Xylene
Methyl t-butyl ether (MTBE)

Urine samples were analyzed for N-Acetyl-S-(phenyl)-L-cysteine, a metabolite of benzene. N-Acetyl-S-(phenyl)-L-cysteine is also known as S-phenylmercapturic acid or PMA. Creatinine was measured in urine using an automated colorimetric method.

The passive air samplers were analyzed by Bureau Veritas (Novi, Michigan), a contract laboratory that is certified by the American Industrial Hygiene Association (AIHA). The samples were analyzed for the following chemicals using the National Institute for Occupational Safety and Health (NIOSH) Method 1501 (NIOSH, 2003).

Benzene
Toluene
Ethylbenzene
ortho-Xylene
meta- and para-Xylene
Methyl t-butyl ether (MTBE)

Results

Participants in the Exposure Investigation

ATSDR conducted the field activities for this EI on March 22-25, 2010. During this time, we collected blood samples from 45 residents of the Hillcrest community and 45 residents of the Dona Park community for a total of 90 participants from 50 separate households. Urine samples were collected from 88 participants, as two of the participants did not provide a urine sample. Passive air samplers were collected from 88 participants, as two of the participants lost or discarded their samplers.

The age of the participants ranged from 7 to 91 years of age, with five of the participants being under the age of 18. Most of the participants were older adults, and the average age of the test population was about 56 years old. The age distribution of the participants reflects the recruitment bias for people who spend much of the day at home in their community. Many of these people were retired or disabled.

Based on information provided from the questionnaires, 46 of the participants self-reported their ethnicity as being Hispanic or Latino. The self-reported race of the participants was: American Indian or Native Alaskan – 2, Black or African American – 30, and White – 58.

Field Conditions during the Exposure Investigation

Wind Direction

The wind rose charts in Appendix B show the wind direction during March 22 to March 25, 2010. These charts were prepared from meteorological data collected at air monitoring stations located near Hillcrest and Dona Park and operated by the Corpus Christi Regional Office of the Texas Commission on Environmental Quality (TCEQ).

As indicated, the wind direction was variable during the EI test period. On March 25, the predominant wind direction was from the northwest, that is, from the refineries toward the Hillcrest and Dona Park communities. On March 22, the wind was blowing part of the day from the northeast, that is, from the refineries toward the Hillcrest and Dona Park communities. During the rest of the sampling period, the wind direction was predominantly from the southeast, that is, from the communities toward the refineries. Therefore, for some of the time, winds would have carried emissions from the refineries toward the communities. For the rest of the time, winds would have carried motor vehicle emissions from Interstate 37 and urban air pollution from downtown Corpus Christi toward the communities.

The map in Appendix C shows the location of the Hillcrest and Dona Park communities in relation to the surrounding oil refineries.

Ambient Air Benzene Concentrations

The Oak Park air monitoring station (see map in Appendix C), located less than 1-mile southwest of the Hillcrest community, is the closest station where ambient air concentrations of benzene are routinely monitored. The University of Texas operates an automated gas chromatogram at this station to measure the ambient air concentration of benzene each hour, 365 days a year. Based on data from this station, the ambient air concentrations of benzene during the EI (March 22-25, 2010) are provided in Appendix D and are summarized below.

Arithmetic mean = 1.27 micrograms per cubic meter ($\mu g/m^3$)[1]
90^{th} percentile[2] = 2.70 $\mu g/m^3$
Maximum = 16.8 $\mu g/m^3$

[1] In this report, the concentrations of benzene and other VOCs in air are reported in units of $\mu g/m^3$. At 20° C and an atmospheric pressure of 760 mm mercury, 1 part per billion of benzene in air equals 3.247 $\mu g/m^3$.

[2] The 90^{th} percentile is a statistical reference point, below which 90 percent of the measured values would fall.

The mean and 90th percentile air benzene concentrations during the EI are similar to ambient air concentrations detected at Oak Park during the previous year (January – December 2009). For January – December 2009, the ambient air concentrations of benzene were:

Arithmetic mean = 1.40 $\mu g/m^3$
90th percentile = 3.38 $\mu g/m^3$
Maximum = 280 $\mu g/m^3$, the next highest = 59.6 $\mu g/m^3$

By comparison, in a survey of 21 urban areas in the United States, the mean benzene concentration in ambient air was about 1 $\mu g/m^3$, based on 24-hour samples (EPA, 2010).

Refinery Activities

ATSDR contacted the refineries in the area and asked them if they were operating during the time period of the EI. At the time of the EI, CITGO's East and West Plants, Flint Hills' East Plant, and Valero's East Plant were all operating under normal conditions. Several units at the Valero West Plant were in startup mode since turnaround, or planned maintenance activities, were completed. Of note, startup is not a period of normal operation in refineries. During this temporary period, plants might potentially have higher emission levels. This is because the pollution abatement equipment may be unable to effectively control emissions when reactor temperatures and process flow rates are below typical operating conditions.

ATSDR contracted with the Eastern Research Group to query the TCEQ Air Emissions Event Report Database for emission events during the month of March 2010. Based on information in this database, three emission events occurred during at least one of the days that the EI was in progress. These emission events included releases of VOCs, including benzene, and are summarized in Appendix E. It is possible that there were other activities that resulted in emissions during this time period, but they did not meet TCEQ's event reporting criteria.

Environmental Testing

Personal Air

ATSDR gave the participants a passive air sampling device (3M™ Organic Vapor Monitor 3500) to measure VOC contaminants in their personal air space. The participants wore their air samplers for a time period of about 48 hours. Two of the participants lost or discarded their air samplers, so samplers from 88 participants were retrieved and analyzed.

The results of the personal air monitoring are presented in Tables 1 and 2. Table 1 indicates that detectable concentrations of benzene were found in 80 of 88 (91 percent) samples. The detection level for benzene varied from 1.9 to 2.1 $\mu g/m^3$ depending on the length of the sampling period. For the other VOCs, the percent of samples with detectable concentrations ranged from 15 percent (ethylbenzene) to 91 percent (toluene). The detection levels for the other VOCs were in the range of 2 to 3 $\mu g/m^3$. In Table 1, samples below the limit of detection are reported as not detected (ND).

Table 1: Number and percent of passive air samplers with detected and non-detected (ND) concentrations of chemical

	Number detected (n_D)	Number non-detected (n_{ND})	Percent detected (n_D/88)
Benzene	80	8	91
Ethylbenzene	13	75	15
m & *p* -Xylene	35	53	40
o -Xylene	26	62	30
Toluene	80	8	91
MTBE	58	30	66

In Table 2, the geometric mean concentrations of VOCs detected by the passive air samplers are compared to personal air sampling data collected from a 1999-2000 National Health and Nutrition Examination Survey (NHANES) (Symanski et al. 2009). These are the most recent, national data available. It is possible that current background exposures to benzene have decreased because of efforts to reduce the benzene content in gasoline and other consumer products and to reduce the exposure of the United States population to environmental tobacco smoke.

NHANES is a program of studies designed to assess the health and nutritional status of adults and children in the United States. The NHANES protocol includes a home interview followed by a standardized physical examination in a mobile examination center. As part of the examination component, blood, urine, and other samples are collected and analyzed for various chemicals. The NHANES test population is selected to be representative of the civilian, non-institutionalized population of the United States.

Table 2 provides the geometric mean concentrations and the 95th percentile confidence intervals for VOCs detected by the passive air samplers from the EI participants. Geometric mean concentrations were not calculated if the concentration of the chemical in 40 percent or more of the samples was below the limit of detection. Using this criterion, we were able to calculate the geometric mean concentrations for two chemicals, benzene and toluene, in blood samples from the EI participants.

Table 2: VOC concentrations (µg/m^3) detected by passive air samplers from EI participants[1]

	EI Range	GM (CI)	GM-NHANES (CI)[2]	N>95th percentile[3]	NHANES 95th percentile[2]
Benzene	ND – 35	3.44 (3.00 – 3.95)	3.21 (2.52 – 3.90)	2 (2%)	18.1
Ethylbenzene	ND – 76	< 2.5	2.93 (2.11 – 3.74)	1 (1%)	25.4
m&p-xylene	ND – 200	< 2.5	7.29 (5.12 – 9.45)	1 (1%)	76.3
o-xylene	ND – 56	< 2.5	2.79 (2.08 – 3.51)	2 (2%)	26.6
Toluene	ND – 390	6.65 (5.48 – 8.07)	17.52 (14.54 – 20.50)	2 (2%)	96.6
MTBE	ND – 0.041	< 2.3	1.4[4]	7 (8%)	21.3[4]

[1] Chemical concentrations below the Limit of Detection (LOD) were calculated as LOD/square root of 2

[2] NHANES values from Symanski et al. 2009

[3] Number of samples greater than the NHANES 95th percentile (percent of samples greater than the NHANES 95th percentile)

[4] NHANES value from Jia et al. 2008

ND = Not detected

Water

ATSDR collected tap water samples from 12 homes. Three of the vials with water samples broke in transit to the laboratory and could not be analyzed. In the remaining 9 water samples, no VOCs were detected in any sample except for a very low concentration (0.013 ng/ml) of MTBE in one sample. The limits of detection for chemicals in the water samples were as follows: benzene (0.024 ng/ml), ethylbenzene (0.024 ng/ml), *m* & *p* – xylene (0.034 ng/ml), *o*-xylene (0.024 ng/ml), toluene (0.025 ng/ml), and MTBE (0.01 ng/ml).

Biological Testing

Blood

The NCEH laboratory analyzed blood samples from 90 EI participants for VOCs using the same analytical procedures with the same detection limits as used in the NHANES testing. The EI test results were compared to data from the 2003-2004 NHANES survey qualitatively in Table 3 and quantitatively in Tables 4 and 5. Table 3 compares the detection frequencies (percent of samples in which the chemical was above the limit of detection) in the EI blood samples and the NHANES blood samples. The NHANES detection frequencies reported in Table 3 were weighted and adjusted for sample design as recommended by the National Center for Health Statistics.

The detection frequencies for all of the BTEX compounds were less for the EI population than for the NHANES population (Table 3). Thus, at the time of blood sample collection, the prevalence of measurable exposures was lower in the test population as compared with the general United States population.

Table 3: Detection frequency (percent detected) for blood VOCs in the EI test population compared with the 2003-2004 NHANES population.

Chemical	EI detection frequency (95^{th} CI)	NHANES detection frequency (95^{th} CI)	P value
Benzene	42 (32-53)	59 (51-66)	< 0.01
Ethylbenzene	28 (19-38)	68 (64-75)	<0.001
m&p-xylene	56 (45-66)	98 (97-100)	<0.001
o-xylene	27 (18-37)	37 (34-40)	0.049
Toluene	80 (70-87)	95 (94-96)	<0.001
2,5-DMF	28 (19-38)	26 (24-29)	0.73

CI = Confidence Interval, which is the range of estimated values that has a 95 percent probability of including the true value of the detection frequency of the population

An additional quantitative comparison was made possible by a recent NCEH analysis of NHANES data that calculated separate reference ranges for smokers and non-smokers. These new data support a more refined analysis of the EI test results, since blood concentrations of VOCs in smokers and non-smokers differ significantly. Tables 4 and 5 provide the geometric mean concentrations and the 95^{th} percentile confidence intervals for VOCs in blood. Geometric mean concentrations were not calculated if the concentration of the chemical in 40 percent or more of the samples was less than the limit of detection.

In this EI report, smokers are defined as those participants with a blood 2,5-dimethylfuran concentration of 0.014 ng/ml or higher. 2,5-DMF is not a constituent of petroleum products. However, it was analyzed because it is a biomarker of exposure to tobacco smoke (Ashley et al., 1996). Low concentrations of 2,5-DMF in blood samples from non-smokers could result from exposure to environmental tobacco smoke.

VOC concentrations below the limit of detection are reported as not detected (ND). The limits of detection for chemicals in the blood samples were the same as in the water samples.

The NHANES surveys, which provided the reference values for the blood VOC concentrations, are conducted in mobile trailers. In a typical NHANES survey, a participant spends an hour or more in the trailer before the blood sample is collected. During this time period, the participant would not be exposed to benzene from automobile exhaust or from smoking. This restriction could result in slightly lower blood VOC concentrations than in random blood samples that had been collected throughout the day. The net effect of this restriction, if any, would be to bias the concentrations of VOCs in smoking EI participants high relative to the NHANES population.

Table 4: Blood VOC concentrations (ng/ml) in non-smoking EI participants (n = 65)

Chemical	EI Range	GM (CI)	GM-NHANES (CI)	N>95th percentile(1)	NHANES 95th percentile(2)
Benzene	ND – 0.081	< 0.024	< 0.024	1 (2%)	0.063
Ethylbenzene	ND – 0.197	< 0.024	0.028 (0.026 – 0.031)	1 (2%)	0.071
m&p-xylene	ND – 0.532	< 0.024	0.122 (0.109 – 0.137)	1 (2%)	0.280
o-xylene	ND – 0.071	< 0.024	<0.024	0	0.081
Toluene	ND – 11.15	0.041 (0.032 – 0.052)	0.082 (0.071 – 0.096)	1 (2%)	0.330
2,5-DMF	ND	< 0.011	< 0.011	0	< 0.011
MTBE	ND – 0.021	< 0.024	NA	0	0.170

GM = Geometric Mean
CI = Confidence Interval
(1) Number of samples greater than the NHANES 95th percentile (percent of samples greater than NHANES 95th percentile)
(2) 95th percentile of Reference Range for non-smokers (2,5-DMF < 0.014) from the 2003-2004 NHANES survey

In Table 4 for blood VOC concentrations in non-smokers, the geometric mean for the EI participants could be calculated only for toluene. As indicated, the geometric mean concentration of toluene in the EI participants was less than the geometric mean concentration in NHANES participants, and the 95th percentile confidence intervals did not overlap. Therefore, the geometric mean concentration of toluene in non-smoking EI participants was significantly less than in NHANES.

Table 5: Blood VOC concentrations (ng/ml) in smoking EI participants (n = 25)

	EI Range	GM (CI)	GM-NHANES (CI)	N>95th percentile(1)	NHANES 95th percentile(2)
Benzene	0.034 – 1.037	0.167 (0.117 – 0.238)	0.138 (0.126 – 0.151)	3 (12%)	0.450
Ethylbenzene	ND – 0.286	0.067 (0.049 – 0.094)	0.068 (0.064 – 0.072)	3 (12%)	0.160
m&p-xylene	0.035 – 0.662	0.158 (0.115 – 0.217)	0.212 (0.197 – 0.228)	2 (8%)	0.460
o-xylene	ND – 0.123	0.037 (0.028 – 0.048)	0.048 (0.045 – 0.051)	3 (12%)	0.090
Toluene	0.088 – 2.204	0.391 (0.278 – 0.549)	0.327 (0.294 – 0.364)	3 (12%)	0.940
2,5-DMF	0.018 -0.538	0.075 (0.049 – 0.116)	0.074 (0.067 – 0.082)	2 (8%)	0.260
MTBE	ND – 0.041	< 0.024	NA	0	0.150

GM = Geometric Mean
CI = Confidence Interval
(1) Number of samples greater than the NHANES 95th percentile (percent of samples greater than NHANES 95th percentile)
(2) 95th percentile of Reference Range for smokers (2,5-DMF > 0.014) from the 2003-2004 NHANES survey

In Table 5 for blood VOC concentrations in smokers, the 95th percentile confidence intervals for all the BTEX compounds overlapped. Therefore, it can be concluded that the geometric mean concentrations of these chemicals in the EI and NHANES populations were not significantly different.

ATSDR also conducted a multiple regression analysis to investigate several factors (independent variables) that could possibly affect blood VOC concentrations. The factors that were used as independent variables were: gender (male, female), race/ethnicity (Hispanics, non-Hispanic whites, non-Hispanic blacks), smoking status based on 2,5dimethylfuran levels (smoker, non-smoker), age, exposure to fuels - such as pumping gas within the past 24-hours (yes, no), time spent indoors (≤ 14 hours, > 14 hours), and distance of home from the refineries. In addition, separate models were fitted with gender and other variables excluding race/ethnicity in one model, and with race and other variables excluding gender in the other model. In a preliminary analysis, we found that toluene was the only blood VOC that was detected above the limit of detection in at least 60 percent of the samples. Therefore, the models were fitted only for this dependent variable. Blood toluene concentrations were log normalized before using them in the models. All observations below the LOD were imputed as LOD/square root of 2. SUDAAN Proc REGRESS was used to fit the models. Analyses were adjusted for possible clustering of cases in homes. The findings from this analysis are presented in the Discussion section of this report.

Urine

The NCEH laboratory analyzed urine samples from 88 participants for PMA (a metabolite of benzene) and creatinine. The analyses were conducted using published analytical procedures (Ding et al. 2009). In the table below, the concentrations of PMA are normalized to the urinary concentration of creatinine to correct for urinary dilution. Only six of the urine samples analyzed had a PMA concentration above the limit of detection (two smokers and four non smokers). Samples below the limit of detection are reported as not detected (ND). The limit of detection for PMA in urine was 0.6 ng/ml.

Table 6: Urine PMA concentrations (µg/g creatinine) in EI participants

Non Smokers (n= 63)			Smokers (n = 25)		
Range	N > CR[1]	CR[2]	Range	N > CR[1]	CR[2]
ND – 1.02	4	ND – 0.45	ND – 0.751	0	ND – 18.4

CR = Comparison Range
[1] Number of samples greater than Comparison Range
[2] Comparison Range from Ding et al. 2009

Quality Control/Quality Assurance Procedures

Appendix F of this report describes the quality control/quality assurance procedures that the NCEH laboratory used to ensure the quality of the data for the blood, urine, and tap water analyses. Quality control/quality assurance procedures for analyzing the passive air samplers are described in NIOSH Method 1501 (NIOSH, 2003).

Discussion

Benzene is a constituent of gasoline and other petroleum products. For the general population, other important sources of benzene exposure are automobile exhaust and cigarette smoke (Wallace, 1996; ATSDR, 2007). Pumping gasoline at a service station is also a source of short-term, but high-level exposures to benzene and other VOCs (Backer et al.1997). In the Hillcrest and Dona Park neighborhoods, it is possible that stack emissions and fugitive emissions from nearby petroleum refineries could also contribute to benzene exposures.

Benzene is the most toxic of the VOCs that were tested in this EI, so it is the focus of the following discussion. However, evaluating exposures to other VOCs can also be useful, since this information may indicate exposure to fuels, refinery emissions, or other consumer products containing VOCs.

Environmental Testing

Personal Air

Benzene

Several published studies of environmental exposure to benzene have documented that personal air concentrations of benzene exceed indoor air concentrations of benzene, which in turn, exceed outdoor air concentrations (Wallace 1996). For example, in a study of three urban neighborhoods in Minneapolis/St. Paul, the median concentrations of benzene in air were 3.2, 1.9, and 1.3 $\mu g/m^3$ for personal, indoor, and outdoor air samples (Sexton et al. 2004). Similar results have been reported in other urban communities (Payne-Sturges et al. 2004). Indoor and personal air concentrations of benzene often exceed outdoor ambient air concentrations because of the contribution of benzene from tobacco smoke and benzene released from paints, adhesives, and other consumer products used in the home.

The geometric mean concentration of benzene in personal air samples was slightly higher in the EI population as compared to an NHANES population (Table 2). However, the overlapping confidence intervals of the geometric means of the EI and NHANES data indicate that the geometric means were not statistically different. The concentration of benzene detected in 86 of 88 (98%) of the personal air samples was less than the 95^{th} percentile of the NHANES reference range (Table 3). Two of the personal air samplers detected an air benzene concentration that exceeded the NHANES reference range. The highest concentration of benzene detected by a personal air sampler in the EI was 35 $\mu g/m^3$. This value slightly exceeds ATSDR's acute Minimal Risk Level (MRL) of 30 $\mu g/m^3$ for benzene. An MRL is protective of human health for non-cancer health effects for continuous exposures of 14 days or less. Although the benzene concentration detected by this personal air sampler slightly exceeded the acute MRL, the benzene concentration was 1/250 of the Lowest Adverse Effect Level – Human Equivalent Concentration that the MRL was based on (ATSDR, 2007). Therefore, breathing this concentration of benzene for 14 days or less is not expected to harm human health. Nevertheless, ATSDR recommends that people should minimize their exposure to benzene by avoiding contact with fuels and other consumer products containing petroleum solvents.

The participant with the highest personal air benzene concentration indicated that she had recently washed her hands with gasoline to remove spray paint, which is a possible short-term source of the elevated air benzene concentration.

None of the other air samplers detected a benzene concentration in excess of ATSDR's acute MRL and are therefore not at levels of health concern for short-term exposures. For illustrative purposes, ATSDR compared the benzene concentrations from the personal air samplers to ATSDR's chronic MRL for benzene (10 $\mu g/m^3$). A chronic MRL is protective of human health for non-cancer health effects for continuous lifetime exposure. Four additional air samples exceeded the chronic MRL for benzene, and one of these samples also exceeded the 95th percentile NHANES air concentration (18 $\mu g/m^3$). However, these air samples were collected over a period of 48 hours, so it is not appropriate to draw health conclusions based on comparison to a guideline developed for continuous, lifetime exposure. In order to assess the risk posed by chronic exposure to contaminants in air, it would be necessary to evaluate contaminant concentrations that are representative of long-term exposures. ATSDR's forthcoming public health assessment will assess the health impact of chronic exposure to benzene and other VOCs.

Other VOCs

Table 2 provides the geometric mean concentrations and the 95th percentile confidence intervals for VOCs detected by the passive air samplers from the EI participants. As indicated by the non-overlapping confidence intervals, the geometric mean concentration of toluene in the EI participants was significantly less than the geometric mean concentration in NHANES participants. This same finding was observed in blood samples, where the geometric mean concentration of toluene in the non-smoking EI participants was less than in NHANES (Table 4). The geometric mean concentrations of the other BTEX chemicals in personal air samples from the EI participants were not significantly different than the NHANES population.

None of the passive air samplers detected a VOC concentration in excess of an ATSDR acute MRL. Therefore, breathing these concentrations of VOCs for 14 days or less is not expected to harm people's health.

One air sampler detected a high concentration toluene (390 $\mu g/m^3$) that was above the NHANES 95th percentile reference range (97 $\mu g/m^3$). However, this concentration of toluene was below ATSDR's acute MRL of 4,000 $\mu g/m^3$ and would not be expected to cause an adverse health effect for short-term exposures. The concentration of toluene in this one personal air sample exceeded ATSDR's chronic MRL for toluene (300 $\mu g/m^3$). However, as discussed previously, it is not appropriate to draw a health conclusion for a short-term air sample compared to a guideline derived for continuous lifetime exposure. The source of toluene exposure for this participant could not be identified. There was no apparent source of toluene exposure from the participant's job. Furthermore, an air sampler worn by another person in the same house did not detect a high toluene concentration.

The results in Table 2 indicate that between 1 and 2 percent of the air samplers detected a BTEX concentration that exceeded the 95th percentile of an NHANES population. Several of the

passive air samplers (8%) detected a concentration of MTBE in excess of the NHANES 95th percentile. Studies of other urban areas have reported that concentrations of MTBE in personal air samples were higher than those reported in NHANES (Payne-Sturges et al. 2004; Jia et al. 2008). It has been suggested that these differences might result from the differential use of MTBE in gasoline in different areas of the country (Jia et al. 2008).

Water

Benzene and Other VOCs

Residents of Hillcrest and Dona Park obtain their drinking water from the same public water system. As a public water utility, it is required to periodically test the water for chemical and microbiological contamination. In this EI, a trace concentration of one VOC (i.e., MTBE) was detected in one of nine tap water samples. MTBE is not a naturally-occurring constituent of petroleum products. However, it has been added to gasoline as an oxygenate to increase the octane rating. MTBE was detected in one tap water sample at a concentration of 0.013 µg/L.

This concentration is far below the U.S. EPA's drinking water advisory of 20-40 µg/L, which is based primarily on taste and odor considerations. The EPA noted that this range is "20,000 to 100,000 (or more) times lower than the range of exposure levels in which cancer or non-cancer effects were observed in rodent tests" (EPA, 1997). Therefore, no VOCs were detected in drinking water samples at concentrations that pose a public health hazard.

Biological Testing

Blood Testing

Benzene

After a person inhales air that contains benzene, the concentration of benzene in the person's blood rapidly increases. After the exposure stops, the concentration of benzene in the person's blood rapidly decreases. Some of the benzene is exhaled in expired breath, some is metabolized and excreted in the urine, and some is transported to other tissues in the body where it may slowly diffuse back into the blood. In experimental studies, human volunteers in a chamber breathed a relatively high concentration of benzene in air (5.2 milligrams per cubic meter (mg/m^3)) for 4-hours (Pekari et al. 1992). After the exposure stopped, the benzene concentration in the blood rapidly decreased. The decrease in blood benzene concentration followed a two phase curve: the elimination half-life for the first phase was 20 to 60 minutes, and the elimination half-life for the second phase was 3 to 6 hours. Therefore, blood benzene concentrations largely reflect recent exposures, and exposures that occurred more than 24 hours ago would have little impact on blood benzene concentrations.

As indicated by the data in Table 4, the geometric mean concentrations of benzene in blood samples from the non smokers in the EI and NHANES population were both below the limit of detection (< 0.024 ng/ml). Therefore, no statistical comparisons could be made. As indicated in Table 5, the confidence intervals for the geometric mean concentrations of benzene in blood from EI smokers and NHANES smokers overlapped. Therefore, it can be concluded that the

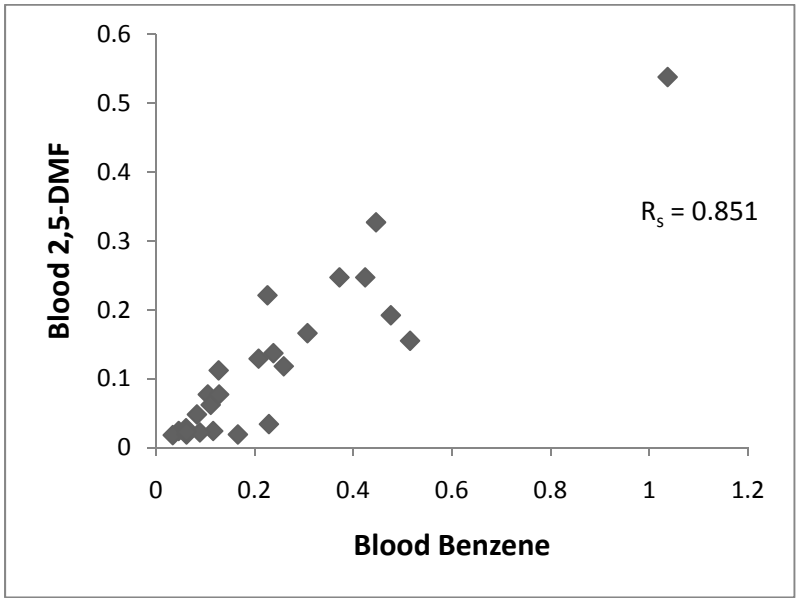
geometric mean concentrations of benzene in these two populations was not statistically significantly different.

In this investigation, blood benzene concentrations were elevated above the 95th percentile of the NHANES reference range in one of 65 non-smokers and three of 25 smokers. The geometric mean concentration of benzene in blood samples from smokers (0.167 ng/ml) was higher than the concentration in blood samples from non-smokers (<0.024 ng/ml). This finding is expected because smoking is known to be a source of exposure to benzene and other VOCs (Ashley et al. 1995; Churchill et al. 2001). The concentrations of benzene in blood samples from cigarette smokers were within the range detected in cigarette smokers from the general population with no occupational exposure to benzene (Brugnone et al. 1992) and were also within the range of benzene concentrations detected in smokers (0.025 – 1.1 ng/ml) in the NHANES population.

It should be noted that the circumstances under which the blood samples were collected from the EI participants might have biased the results high relative to the NHANES population. The EI blood samples were collected from people in their homes where they may have recently smoked a cigarette. Under these circumstances, the blood levels of benzene, toluene, ethylbenzene, xylenes and 2,5-DMF from the tobacco smoke would have been near the maximum. By comparison, NHANES blood samples are collected at a mobile exam center where tobacco smoking is prohibited. Thus, the NHANES blood VOC data would not be influenced by tobacco smoke exposure within the previous 1 to 3 hrs, whereas the EI exposure data could be.

In Figure 1, the blood concentration of 2,5-DMF, a biomarker for exposure to tobacco smoke, is plotted against the blood concentration of benzene for the 25 EI participants who were classified as smokers. The Spearman rank correlation coefficient for this relationship is 0.851 ($p < 0.001$). This high and statistically significant correlation coefficient suggests that exposure to tobacco smoke is a major source of benzene exposure in the EI participants who were smokers.

Figure 1. Concentration of 2,5-dimethylfuran in blood (ng/ml) vs. concentration of benzene in blood (ng/ml)



ATSDR also examined the correlation between blood benzene concentrations and air benzene concentrations from the personal air monitors. For smokers, the Spearman rank correlation coefficient for this relationship was 0.340 ($p = 0.101$). For the total EI population (smokers and nonsmokers), the Spearman rank correlation coefficient was lower: 0.129 ($p = 0.435$). This low correlation could be due to the fact that the air monitors measured the benzene air concentrations over a 48-hour monitoring period, whereas blood benzene concentrations are highly influenced by benzene exposures that occurred within a few hours of blood collection. Other studies have also reported a low correlation between concentrations of benzene in blood and personal air samples, with the correlation in smokers being higher than in nonsmokers (Lin et al. 2008).

The participants in this EI included five children under the age of 18. Four of the children did not have a detectable concentration of benzene in their blood samples, and one child had a benzene concentration (0.042 ng/ml) that was less than the 50th percentile of blood benzene concentration reported in children (Sexton et al. 2005 and Sexton et al. 2006). In the general population, blood benzene concentrations in children are similar to those in adults except at the high end of the exposure range, where adults have higher levels than children (Sexton et al. 2005, Sexton et al. 2006). The higher blood benzene concentrations in adults at the 90th and 95th percentiles are likely due to cigarette smokers in the adult population.

The NHANES reference range for benzene is based on a statistical analysis of blood benzene concentrations detected in a representative sample of the United States population. In this EI, we considered blood benzene concentrations in excess of the NHANES 95th percentile to be elevated as compared to the United States population. However, the NHANES 95th percentile is not a health-based value, so it cannot be concluded whether blood benzene concentrations in excess of the 95th percentile do or do not pose a public health hazard. Also, a blood benzene concentration detected during this EI at one point in time may not be representative of long-term exposures.

It should also be recognized that, by definition, 5 percent of the people in the NHANES population exceeded the 95th percentile. Therefore, it is to be expected that some of the EI participants would also exceed the NHANES 95th percentile.

In the Personal Air Testing section of this report, it was noted that one participant had a relatively high personal air monitor reading of 35 $\mu g/m^3$ for benzene. However, the blood benzene concentration in this person was less than the limit of detection. These findings could be explained by the fact that a likely source of the participant's exposure to benzene (spray painting and washing her hands with gasoline) occurred more than 24 hours before the blood sample was collected. As discussed previously, blood benzene concentrations are largely determined by recent exposures. High blood concentrations in participants with relatively low air benzene concentrations could occur if a person smoked a cigarette shortly before donating a blood sample.

Blood Benzene Concentrations on Day 1 vs. Day 2

ATSDR also compared benzene concentrations in blood samples (n = 47) collected on March 24 (day 1 of the blood testing) to blood samples (n = 43) collected on March 25 (day 2). On March 24, the predominant wind direction was from the communities toward the refineries, whereas on

March 25, the predominant wind direction was from the refineries toward the communities (Appendix B). Furthermore, as indicated by the data in Appendix D, the ambient air concentrations of benzene at the Oak Park monitoring station were higher on March 25 (mean = 2.66 $\mu g/m^3$), as compared to March 24 (mean = 0.26 $\mu g/m^3$).

To compare the blood benzene concentrations for these two days, ATSDR conducted a modified t test (Welch test). A Welch test is a nonparametric statistical test that evaluates the mean of two test groups of unpaired data relative to the variability of their scores. The mean (average) blood concentration of benzene for all participants on March 24 was 0.0977 ng/ml, and on March 25, 0.0597 ng/ml. These results indicate that blood benzene concentrations were higher when the predominant wind direction was from the communities toward the refineries and lower when the predominant wind direction was from the refineries toward the communities. Although the mean blood benzene concentration was higher on day 1 than on day 2, the difference was not statistically significant ($p = 0.227$).

In this EI, cigarette smoking was shown to be an important source of benzene exposure. Therefore, we repeated the comparison of blood benzene concentrations on day 1 and day 2 after removing smokers from the EI population. Under these conditions, the mean blood benzene concentration on day 1 in the non-smoking EI participants was 0.0191 ng/ml, and on day 2, 0.0189 ng/ml. The difference between day 1 and 2 was not statistically significant ($p = 0.928$).

Therefore, these test results provide no evidence that blood benzene concentrations were higher on March 25, when the wind was blowing from the refineries toward the communities (air benzene = 2.66 $\mu g/m^3$) as compared to March 24, when the wind was blowing from the communities toward the refineries (air benzene = 0.26 $\mu g/m^3$).

Other VOCs

The other, less toxic VOCs in blood showed a pattern similar to what was seen with benzene – i.e., blood concentrations in smokers were higher than concentrations in non-smokers. Most of the VOC concentrations that exceeded the NHANES 95th percentile value were detected in blood samples from smokers. Cigarette smoking is known to be a source of exposure to ethylbenzene, xylenes, and toluene. Only one non-smoking EI participant had a blood VOC concentration that exceeded the NHANES 95th percentile for non-smokers (Table 4). The blood sample from this participant had a high concentration of toluene (11.1 ng/ml), as well as elevated concentrations of ethylbenzene (0.197 ng/ml) and *m*- and *p*-xylene (0.532 ng/ml), and a benzene concentration below the limit of detection. The personal air monitor from this participant also detected an elevated concentration of toluene in air (discussed previously). Toluene is a constituent of gasoline and other petroleum fuels and is found in a wide variety of consumer products including adhesives, paints, paint thinners, furniture polishes and cleaners, lacquers, inks, floor polish, etc. However, no source of toluene exposure for this person could be identified.

As discussed previously, ATSDR conducted a multiple regression analysis to investigate factors that could possibly affect blood toluene concentrations in the EI population. Among the variables tested, age ($p=0.52$), fuel use (e.g., pumping gas) ($p=0.80$), and time spent indoors ($p=0.47$) were not found to be statistically significantly associated with blood toluene concentrations. Blood toluene concentrations increased with an increase in distance between the

refineries and homes (p=0.01, slope=0.0008). No gender differences were found (p = 0.63), adjusted GM_{males}= 0.076 ng/mL (95% CI: 0.056-0.102), $GM_{females}$= 0.083 ng/mL (95% CI: 0.068-0.102). Non-smokers were found to have statistically significantly lower levels of blood toluene than smokers (p < 0.001, adjusted $GM_{smokers}$ = 0.372 ng/mL (95% CI: 0.254-0.545), $GM_{non\text{-}smokers}$ = 0.042 ng/mL (95% CI: 0.033-0.0.527). Race/ethnicity was not found to be a statistically significant factor affecting toluene concentrations (adjusted $GM_{Hispanics}$ = 0.076 ng/mL (95% CI: 0.048-0.121), $GM_{NH\text{-}White}$ = 0.104 ng/mL (95% CI: 0.071-0.153), $GM_{NH\text{-}Blacks}$ = 0.072 ng/mL (95% CI: 0.047-0.112).

Thus, smoking status and distance between a person's home and a refinery were the only independent variables that were significantly associated with blood toluene concentrations. Smokers had statistically higher blood toluene concentrations than non-smokers. The results also indicated that blood toluene concentrations were lower in people living near the refineries than in people living further away. This finding suggests that the refiners were not a source of toluene exposure.

Urine

Benzene is metabolized primarily by the liver, although the bone marrow and other tissues have some capacity to metabolize benzene (ATSDR 2007). Benzene is metabolized primarily to phenol and dihydroxyphenols that are conjugated and excreted in the urine. Although phenols and dihydroxyphenols are the major metabolites of benzene, they are also present in foods, beverages, and over-the-counter medications (McDonald et al. 2001), which can confound interpretation of low level benzene exposures. Small amounts of benzene are also metabolized and excreted in the urine as conjugates of trans, trans-muconic acid and S-phenylmercapturic acid (PMA). PMA in urine is a particularly useful biomarker of benzene exposure, since it is a specific and sensitive biomarker of benzene exposure. Specificity means that PMA is a unique biomarker for benzene and would not be affected by exposure to other related phenols or hydroxyphenols. Sensitivity means that PMA can be detected at low concentrations in the urine.

Summary statistics for the concentration of the benzene metabolite, PMA, in urine samples from the EI participants are presented in Table 6. There is no NHANES reference range for PMA concentrations in urine. In a recent study, Ding et al. (2009) reported on the range of PMA concentrations detected in urine samples from anonymous donors (Table 6). The range of values reported in this study is based on test results from 59 non-smokers and 61 smokers, so the comparison ranges are of moderate confidence. The PMA concentrations detected in the EI participants were generally within these ranges, except for four non-smokers who were outside the reported range. None of these four participants had a detectable blood benzene concentration. The benzene concentrations in the personal air samples from these four participants were also low (< LOD to 3.9 $\mu g/m^3$).

There is no health-based reference value for PMA in the general population. For occupational exposures to benzene, the American Conference of Governmental Industrial Hygienists has recommended a Biological Exposure Index (BEI) for PMA in urine of 25 micrograms per gram ($\mu g/g$) creatinine. The BEI was derived to protect healthy adult workers, so it may not be applicable to all segments of the general population. Nevertheless, the BEI is about 25 times higher than the highest PMA concentration (1.02 $\mu g/g$) detected in an EI participant.

Limitations of Exposure Investigation

The environmental and biological samples from this EI were analyzed using validated analytical methods with rigorous quality assurance/quality control procedures, so the results are of high confidence (Appendix F). Furthermore, the blood and air data were compared to reference ranges from the NHANES surveys. The NHANES population was selected to be representative of the United States population, and the data from these surveys are the most complete and highest quality data available. As previously discussed, the comparison range for the urine data is of moderate confidence because it is based on a smaller comparison population.

The environmental and biological sampling for this EI were conducted on March 22-25, 2010. During this time period, the daily average concentrations of benzene in ambient air at the Oak Park monitoring station were higher than the annual average on 2 days and below the annual average on the other 2 days (Appendix D). Wind direction was variable, although the predominant wind direction was directly from Refinery Row to the communities during one of the two days of blood sampling (Appendix B). At the time of the EI, two of the refineries were operating at normal capacity, and some of the units in a third refinery were in start-up mode, which could result in increased emissions (Refinery Activities and Appendix E).

Given the multiplicity of variables that could affect ambient air concentrations of VOCs, it is not possible to define what constitutes typical exposure conditions. Therefore, ATSDR concludes that the findings of the EI and the resulting conclusions are specific for the time period of the EI. ATSDR draws no conclusions as to exposures that occurred in the past or might occur in the future under different conditions.

The EI was designed as a biased sampling with a preference for residents who lived near Refinery Row and spent much of their time at home. Therefore, the test results from the 90 people who participated in the EI might not be representative of the community-at-large or of other time periods.

Notifying the Community of Test Results

In May, 2010, ATSDR sent a letter to each participant of the EI to notify them of their test results. In addition, ATSDR held an availability session in June, 2010 in Corpus Christi. At this session, the participants could meet with an ATSDR toxicologist or physician to discuss their individual test results.

ATSDR also provided the telephone number for an ATSDR physician or toxicologist that the participants or their health care provider could call to discuss test results.

Child Health Considerations

In the general population, the average background concentrations of benzene in blood in children and in adults are similar (Sexton et al. 2005, Sexton et al. 2006). At the upper end of the background exposure range, blood benzene concentrations in adults are higher than children. This is likely due to benzene exposure from tobacco smoking in adults.

The scientific and medical literature does not provide any clear evidence of age-related differences in susceptibility to benzene toxicity (ATSDR, 2007).

Conclusions

(1) This EI did not confirm the blood benzene test results previously reported by Texas A&M University. It is possible that the measurement procedures used by Texas A&M University produced incorrect test results.

(2) The concentrations of benzene and other petroleum-related VOCs detected in personal air samples from the EI participants were not higher than those detected in residents of the United States in a national survey (NHANES).

(3) There was no evidence of widespread exposure to elevated concentrations of environmental VOCs. Elevated concentrations of VOCs detected in a few personal air samples were possibly due to direct contact with fuels or other consumer products containing petroleum solvents.

(4) In nine tap water samples analyzed, no VOCs were detected at a concentration that posed a public health hazard.

(5) The concentrations of benzene and other petroleum-related VOCs detected in blood samples from the EI participants were not higher than those detected in residents of the United States in a national survey (NHANES).

(6) Blood concentrations of VOCs were higher in EI participants who smoked as compared to EI participants who did not smoke.

(7) Blood concentrations of benzene in smokers were highly correlated with the blood concentrations of 2,5-dimethylfuran, a biomarker of exposure to tobacco smoke. This finding suggests that tobacco smoke is a major source of benzene exposure in smokers.

(8) The conclusions of this health consultation are based on the time period during which this exposure investigation was conducted. This report draws no conclusions regarding past or future exposures to VOCs in the community.

Recommendations

(1) Exposures to benzene and other aromatic hydrocarbons can be reduced by avoiding exposure to tobacco smoke and minimizing exposure to fuels and other consumer products containing petroleum solvents.

(2) Further biological monitoring is not warranted unless new evidence becomes available to document that residents living near the refineries are being exposed to benzene or other VOCs at levels of health concern.

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Appendix A

Purpose	• The Agency for Toxic Substances and Disease Registry (ATSDR) will do an exposure investigation (EI) that focuses on screening for benzene and other petroleum related chemicals in people who live near "refinery row." • ATSDR will test about 100 residents for exposure to these chemicals. • We will test blood, urine, and air that people are breathing. • Participants will get their individual test results and an explanation of what they mean. • ATSDR will release an Exposure Investigation (EI) report that gives a summary of the findings and recommends any follow-up activities needed to protect public health. Participant names will not be included in the EI report.
Who is eligible to participate?	• People who have the highest potential exposures to these chemicals, such as people who live nearest to the refineries and who spend much of the day at home. • Participants from a previous pilot project, a collaborative effort by Texas A&M University and Citizens for Environmental Justice. • Smokers and children are also eligible. • ATSDR will give first choice to households in which two or more people will participate in the testing. • ATSDR will work with the community to identify participants.
What will ATSDR ask the participants to do?	• Complete a short questionnaire. • Complete a time-activity log sheet to evaluate possible sources of exposure to benzene and related chemicals. • Provide blood and urine samples, and wear a personal air sampling badge.
When and where will the testing be done?	• ATSDR will make an appointment for a home visit to obtain a blood, urine and personal air samples at a time that is convenient for the participant.
How can I be tested?	• If you would like to participate in this screening, please call **Dr. Ken Orloff of ATSDR at 1-888-320-5291 to make an appointment**. He can also address questions you have about the screening. There is no cost to you for this testing. ATSDR will send you your individual test results about 6-8 weeks after testing.

CS210798

Appendix B

About Wind Roses:

Air quality is affected by wind direction and speed. Wind roses are diagrams that provide information on wind direction and wind speed over a specified period of time.

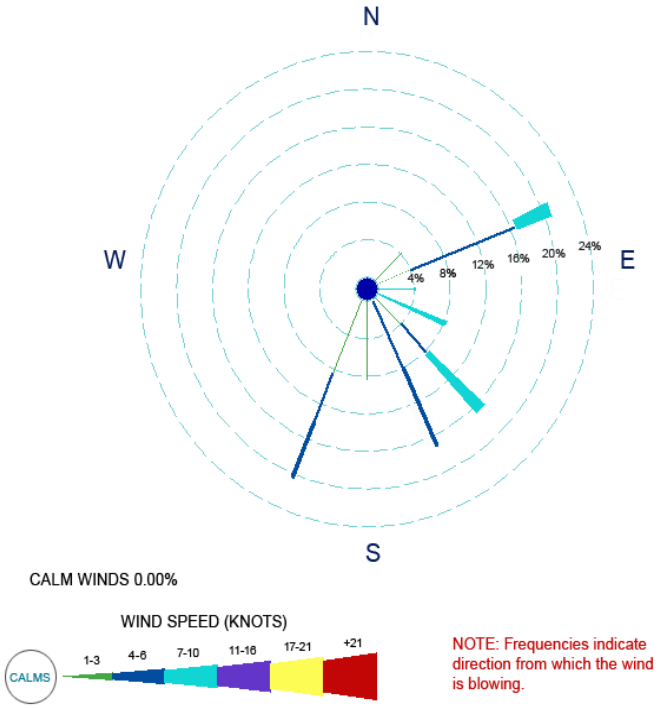
The following text provides information on how to interpret wind roses:

- Each branch of the rose represents wind coming from that direction, with north at the top of the diagram

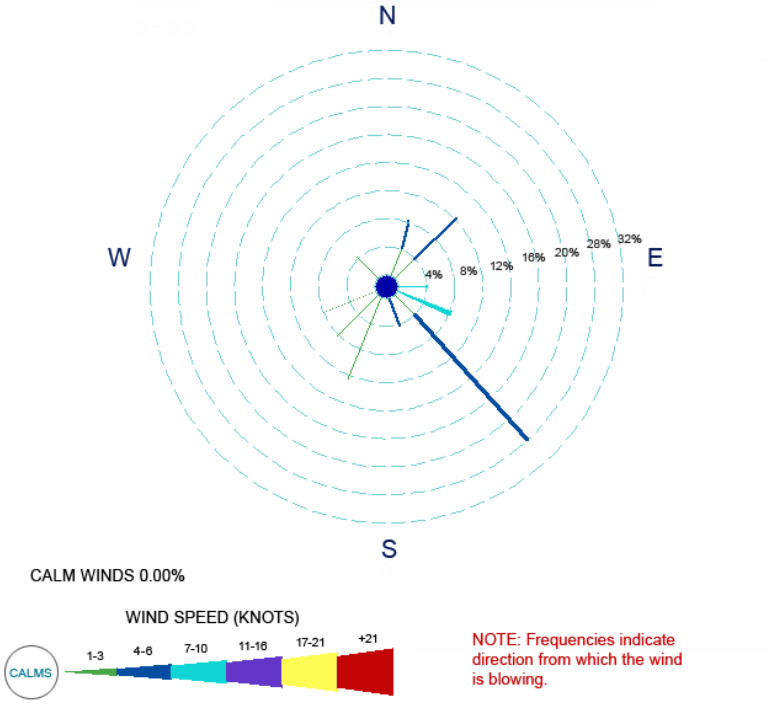
- Each branch is divided into segments of different length and color. The length of each segment is proportional to the percent of time that the wind blows from that direction. The color of the segment indicates the wind speed from that direction.

March 22, 2010

Hillcrest Monitoring Station

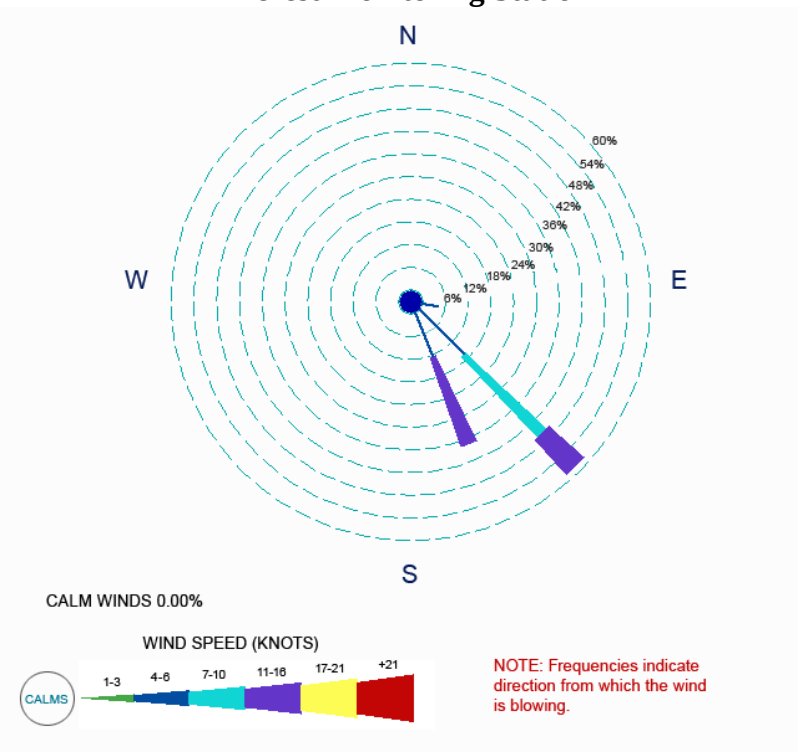


Dona Park Monitoring Station

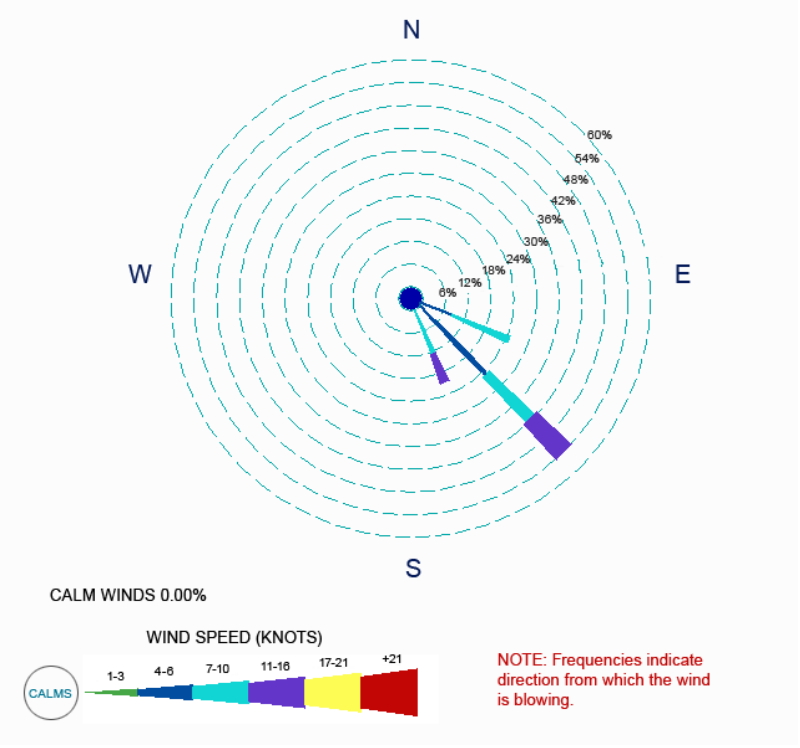


March 23, 2010

Hillcrest Monitoring Station

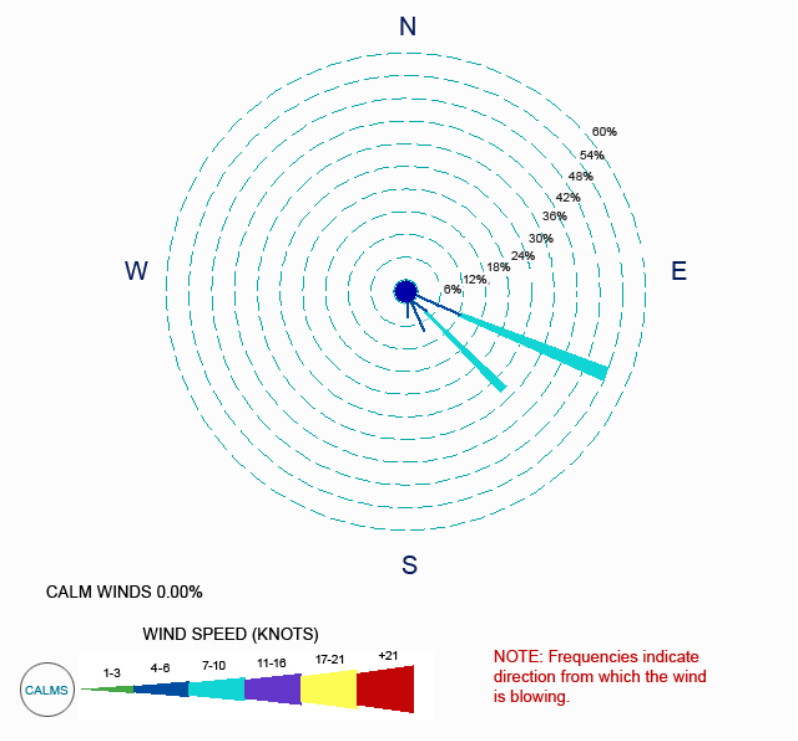


Dona Park Monitoring Station

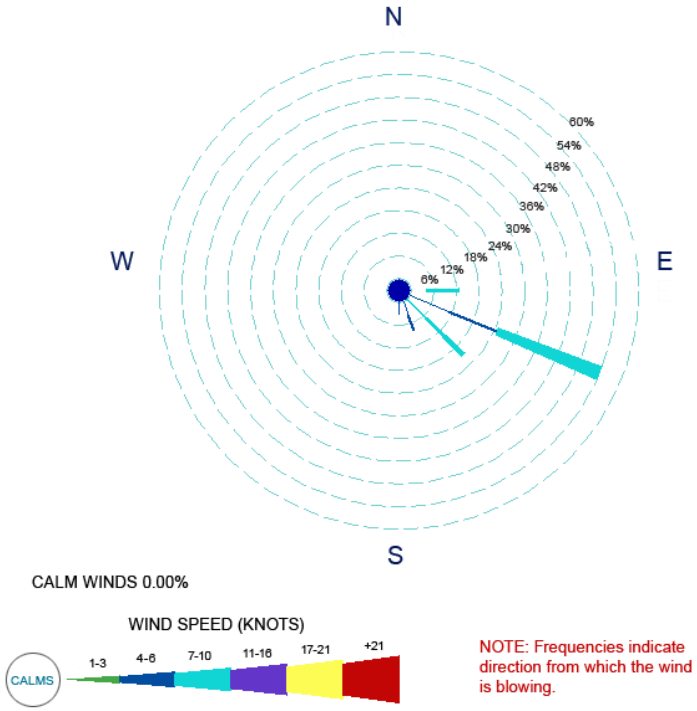


March 24, 2010

Hillcrest Monitoring Station

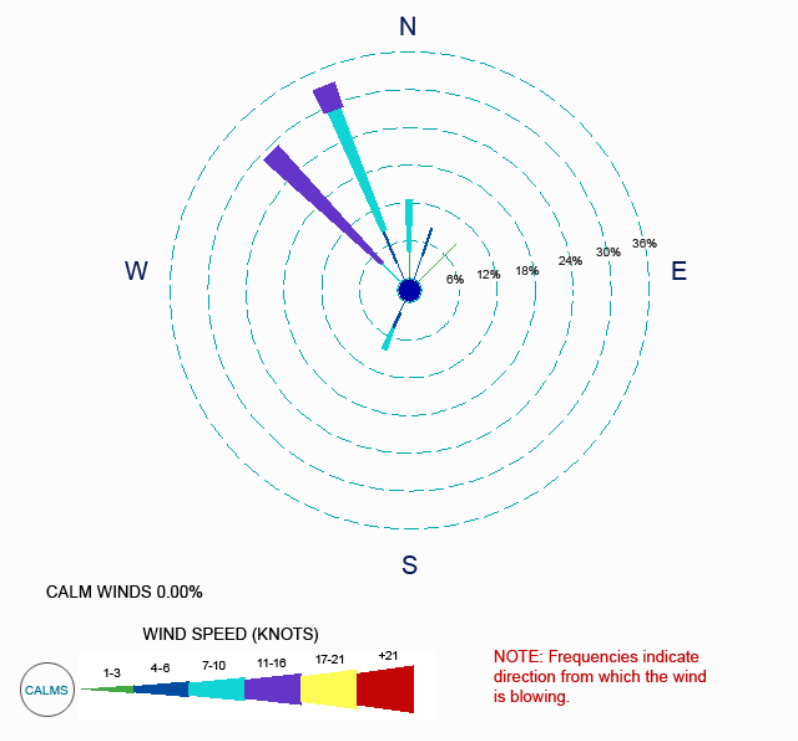


Dona Park Monitoring Station

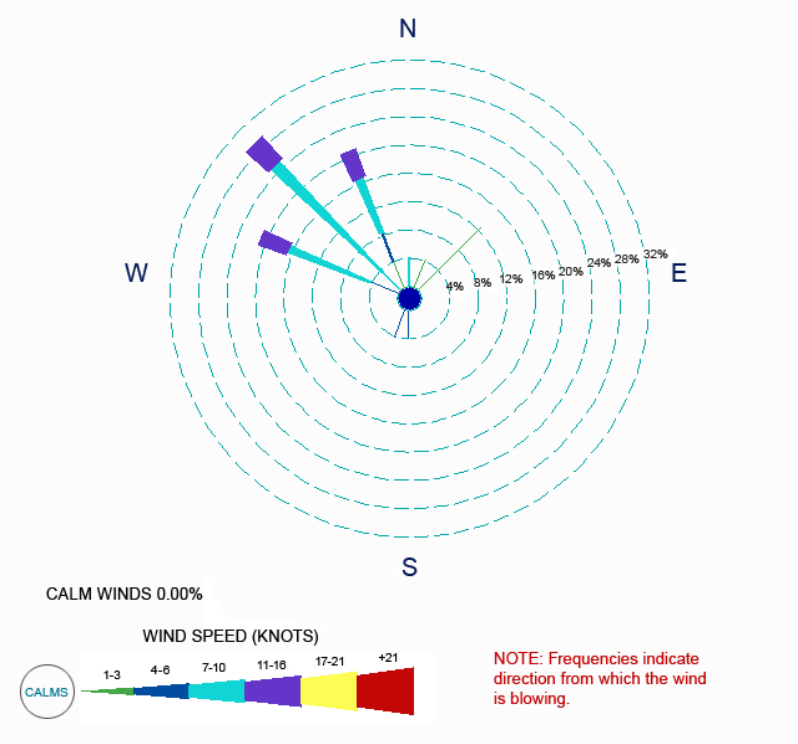


March 25, 2010

Hillcrest Monitoring Station

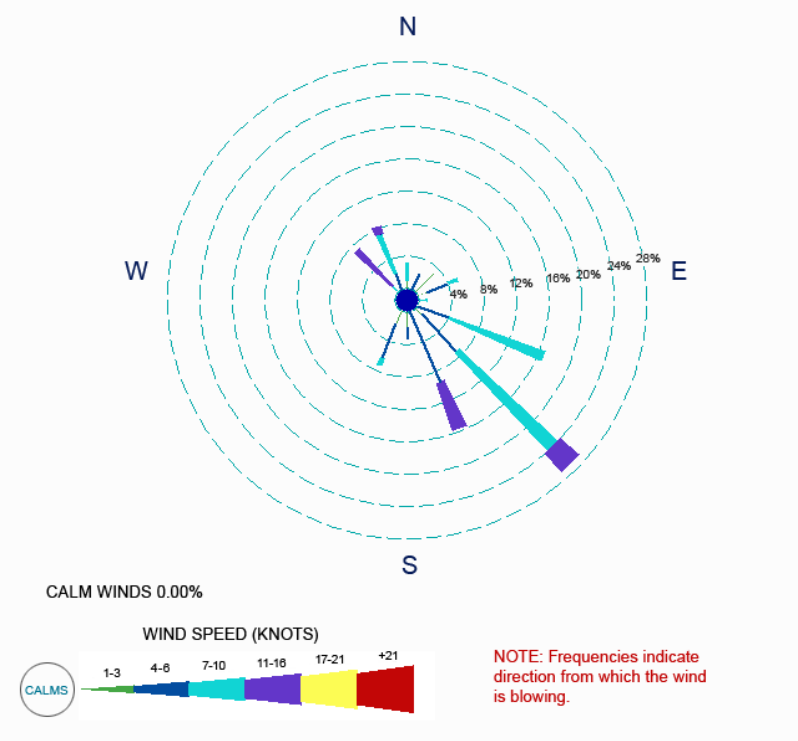


Dona Park Monitoring Station

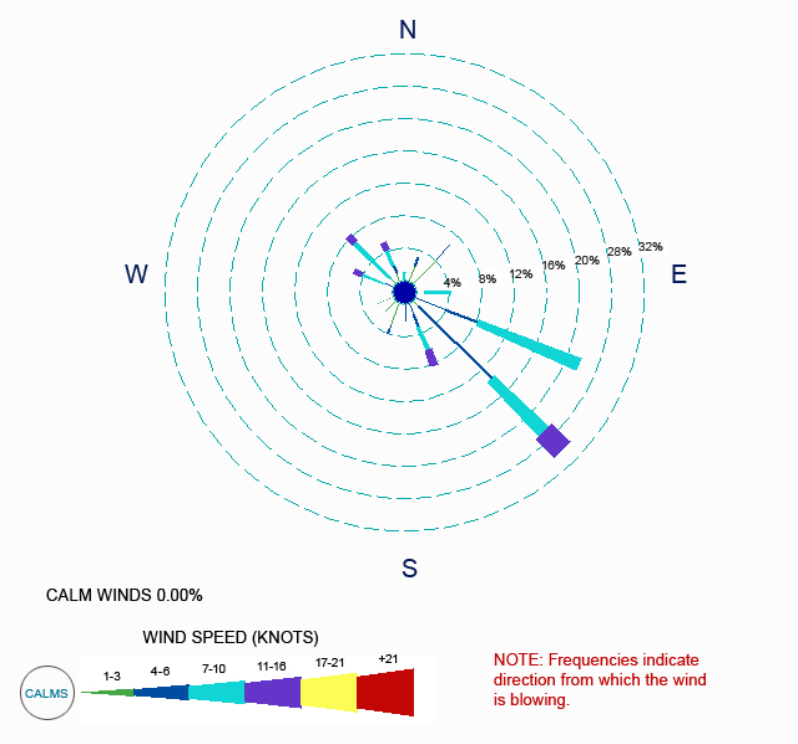


March 22-25, 2010

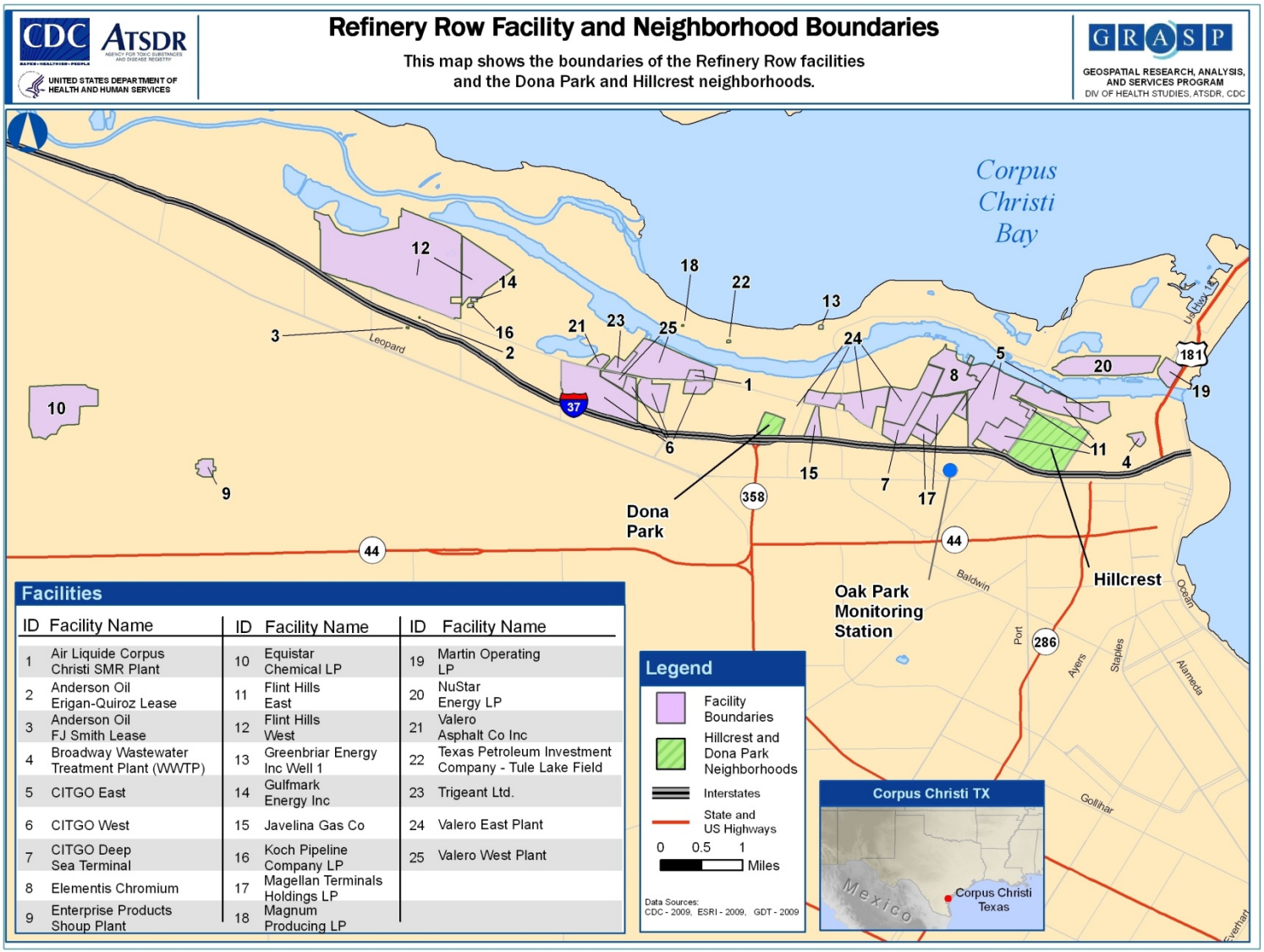
Hillcrest Monitoring Station



Dona Park Monitoring Station



Appendix C


CDC
ATSDR
UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES
Refinery Row Facility and Neighborhood Boundaries
This map shows the boundaries of the Refinery Row facilities and the Dona Park and Hillcrest neighborhoods.
GRASP
GEOSPATIAL RESEARCH, ANALYSIS, AND SERVICES PROGRAM
DIV OF HEALTH STUDIES, ATSDR, CDC
Corpus Christi Bay
Leopard
Dona Park
Oak Park Monitoring Station
Hillcrest
Baldwin
Port
Ayers
Staples
Alameda
Ocean
Gollihar
Everhart
37
44
358
286
181
Facilities
ID Facility Name
1 Air Liquide Corpus Christi SMR Plant
2 Anderson Oil Erigan-Quiroz Lease
3 Anderson Oil FJ Smith Lease
4 Broadway Wastewater Treatment Plant (WWTP)
5 CITGO East
6 CITGO West
7 CITGO Deep Sea Terminal
8 Elementis Chromium
9 Enterprise Products Shoup Plant
10 Equistar Chemical LP
11 Flint Hills East
12 Flint Hills West
13 Greenbriar Energy Inc Well 1
14 Gulfmark Energy Inc
15 Javelina Gas Co
16 Koch Pipeline Company LP
17 Magellan Terminals Holdings LP
18 Magnum Producing LP
19 Martin Operating LP
20 NuStar Energy LP
21 Valero Asphalt Co Inc
22 Texas Petroleum Investment Company - Tule Lake Field
23 Trigeant Ltd.
24 Valero East Plant
25 Valero West Plant
Legend
Facility Boundaries
Hillcrest and Dona Park Neighborhoods
Interstates
State and US Highways
0 0.5 1
Miles
Data Sources:
CDC - 2009, ESRI - 2009, GDT - 2009
Corpus Christi TX
Mexico
Corpus Christi Texas

Appendix D

Benzene concentrations in ambient air at Oak Park monitoring station
(March 22-25, 2010)

Benzene Concentrations ($\mu g/m^3$)					
Hour	22-Mar	23-Mar	24-Mar	25-Mar	Mar 22-25
1	6.23	no sample	0.13	3.25	3.18
2	4.77	no sample	0.1	no sample	2.44
3	no sample	0.29	no sample	no sample	0.78
4	no sample	0.29	no sample	2.44	1.36
5	1.98	0.32	0.23	1.59	1.04
6	3.02	0.42	0.23	1.79	1.36
7	5.55	0.49	0.19	16.82	5.78
8	3.6	0.62	0.42	2.57	1.82
9	1.56	0.45	0.29	2.24	1.14
10	0.65	0.32	0.29	1.82	0.78
11	0.42	0.29	0.23	1.1	0.52
12	0.71	0.29	0.29	1.1	0.62
13	0.52	0.29	0.29	1.07	0.55
14	0.36	0.52	0.23	0.91	0.52
15	0.49	0.26	0.36	0.81	0.49
16	0.29	0.36	0.32	0.88	0.45
17	0.52	0.29	0.26	1.23	0.58
18	0.32	0.29	0.26	2.24	0.78
19	0.42	0.32	0.26	3.47	1.14
20	0.55	0.36	0.29	4.61	1.46
21	0.49	0.26	0.26	5.81	1.72
22	0.45	0.26	0.42	1.69	0.71
23	0.36	0.29	0.19	1.62	0.62
24	0.32	0.16	0.23	1.82	0.65
Maximum	6.23	0.62	0.42	16.82	
Average	1.53	0.32	0.26	2.66	1.27

Appendix E

Emission Events during the EI

Refineries in Corpus Christi experience several different types of events that are reportable to TCEQ. The agency's Air Emission Event Report Database[1] classifies these into at least five categories: emissions event, air startup, air shutdown, excess opacity, and maintenance. To facilitate evaluation of emission events, Eastern Research Group ran queries on TCEQ's database to obtain all emission events reported for Nueces County facilities for the entire month of March. This time frame was selected because some emission events could have started weeks before the EI began. Based on this query, three emission events for Refinery Row facilities occurred on at least one of the days that the EI took place:

- **Flint Hills East (report #136946).** Flint Hills East submitted a final report of increased emissions expected from scheduled maintenance of the facility's Flare Gas Recovery Unit (FRGU). This report indicates that the FRGU was down from noon on March 21 through 6:00 p.m. on March 28. During this time, the facility continued to operate as usual, with the main difference being that process gases typically sent to the FRGU for hydrocarbon recovery were instead vented directly to a flare. This maintenance and shutdown increased facility-wide emissions. Specifically, Flint Hills East estimated that the shutdown increased hydrocarbon emissions by approximately 1,950 pounds. Most of these increased emissions were estimated for "hexane plus" (28%) and carbon monoxide (38%). This activity also released an estimated 8.1 pounds of benzene over the duration of the event.

- **Valero West (report #137342).** The first of two Valero West reportable events was a maintenance event occurring on March 23, beginning at 7:07 a.m. and ending at 9:30 p.m. According to this event's final report, the facility removed a single tank from service for required maintenance. The tank was de-gassed and vapors were routed to a thermal oxidizer. Valero West estimated that 31 pounds of hydrocarbons were released as a result, the majority being "volatile organic compounds" (72%). The estimated increase in benzene emissions was 0.14 pounds.

- **Valero West (report #136778).** The second Valero West reportable event was an air startup event beginning at 2:40 p.m. on March 14 and ending at 5:40 p.m. on April 1. According to this event's final report, which has limited detailed information, Valero West experienced emissions from startups of "various equipment" during scheduled maintenance in three of the plant's "complexes." The facility estimated emissions during the startup were intermittent throughout the 20-day period and amounted to approximately 8,230 pounds, the majority being carbon monoxide (32%) and isopentane (18%). No estimated benzene emissions were reported.

[1] These data can be accessed at: http://www11.tceq.state.tx.us/oce/eer/index.cfm.

Appendix F

Quality Control/ Quality Assurance data for analysis of blood VOCs and urine VOC metabolites

Analytical Blanks

VOCs are particularly challenging chemicals to measure because they are found in many plastics and other materials at low levels. Additionally, they evaporate easily and can move through the air to new locations. Therefore, our analysis of VOCs in blood included analysis of samples that we know contain no VOCs (blanks) to be sure that any VOCs measured came from the blood sample and not from contamination. Each batch of blood samples analyzed included several different analytical blanks. In Table D1 we show our results from the three batches of analyses that included blood samples from Corpus Christi. No analytical blanks contained detectable levels of any of the target VOCs; therefore we conclude that there was no significant contamination of the target VOCs during the analysis.

Table D1: Summary of analytical blanks analyzed along with Corpus Christi EI blood and water samples

Analyte Code	# Method Blanks Analyzed	LOD	# Blank Results >LOD
2DF	22	0.0112	0
VBZ	20	0.0242	0
VEB	21	0.024	0
VME	22	0.01	0
VOX	22	0.024	0
VTO	20	0.025	0
VXY	22	0.0335	0

Similarly, each batch of urine samples analyzed included two analytical blanks. In Table D2 we show our results from the two batches of analyses that included urine samples from Corpus Christi. No analytical blanks contained detectable levels of any of the target VOC metabolites; therefore we conclude that there was no significant contamination of the target VOC metabolites during the analysis.

Table D2: Summary of analytical blanks analyzed along with Corpus Christi EI urine samples

Analyte Code	# Method Blanks Analyzed	LOD	# Blank Results >LOD
PMA	4	0.6	0

Analytical Accuracy

Before we analyzed any samples from Corpus Christi, we made sure that our methods were accurate. This means that we evaluated our methods with test samples that contained a known amount of target VOCs, to make sure that our answers were acceptably close to the correct answers. This process is called proficiency testing (PT). To do this, an independent quality control officer at CDC blind coded samples containing known amounts of VOCs and then gave them to the VOC Lab to analyze. We analyzed these samples without knowing the VOC levels, and reported the results back to the quality control officer. He then compared the levels we reported with the true levels. If the reported results were within 25% of the true results for ≥80% of the PT samples, then the method was acceptably accurate and passed PT. As shown in Table D3, both the blood VOC method and the urine VOC metabolite method were acceptably accurate for all reported analytes.

Table D3: Proficiency testing data indicates that methods have acceptable accuracy.

Test Date	Analyte Code	Pass?, ≥80% within 25% of true	Passed, by Analyte
12/22/2009	2DF	Yes	5/5
12/22/2009	VBZ	Yes	5/5
12/22/2009	VEB	Yes	5/5
12/22/2009	VME	Yes	5/5
12/22/2009	VOX	Yes	4/5
12/22/2009	VTO	Yes	5/5
12/22/2009	VXY	Yes	5/5
2/17/2010	PMA	Yes	5/5

Analytical Precision

When we analyzed the blood and urine samples from Corpus Christi we made sure that the methods were acceptably precise. In other words, we made sure that our measurements were reproducible, so that measuring the same sample multiple times gave us the same approximate

analytical result. To confirm acceptable analytical precision during each batch of sample analysis we analyzed quality control (QC) samples of known analyte concentration. We evaluated the method precision based on the following rules:

1) If both QC run means are within 2Sm limits and individual results are within 2Si limits,then accept the run.
2) If 1 of the 2 QC run means is outside a 2Sm limit - reject run if:
   - Extreme Outlier – Run mean is beyond the characterization mean +/- 4Sm
   - 1 3S Rule - Run mean is outside a 3Sm limit
   - 2 2S Rule - Both run means are outside the same 2Sm limit
   - 10 X-bar Rule – Current and previous 9 run means are on same side of the characterization mean
3) If one of the 4 QC individual results is outside a 2Si limit - reject run if:
   - R 4S Rule – Within-run ranges for all pools in the same run exceed 4Sw (i.e., 95% range limit)
   - Note: Since runs have multiple results per pool for 2 pools, the R 4S rule is applied within runs only.

Abbreviations:

- Si = Standard deviation of individual results (the limits are not shown on the chart unless run results are actually single measurements).
- Sm = Standard deviation of the run means (the limits are shown on the chart).
- Sw = Within-run standard deviation (the limits are not shown on the chart).

Relevant Date-Batch ranges for the Corpus Christi EI:

Assay ID	Analysis Date	Run Within Day	Batch ID	Study ID
MERCAP	03/27/2010	1	S10085B	VOC-CorpusChristiBz10-41
MERCAP	03/29/2010	1	S10087B	VOC-CorpusChristiBz10-41

Analysis Date	Assay ID	Run Within Day	Batch ID	Study ID
03/30/2010	VOC36	1	R10089	VOC-CorpusChristiBz10-41
04/05/2010	VOCW	1	B10095	VOC-CorpusChristiBz10-41
04/05/2010	VOC36	2	A10095	VOC-CorpusChristiBz10-41

The quality control material had acceptable precision for all analytes reported for this study.

Codes for Volatile Organic Compounds (VOCs) and Metabolites

Code	Analyte name
PMA	N-acetyl-S-(phenyl)-L-cysteine
WBZ	Benzene in water
WXY	m-/p-xylene in water
WOX	o-xylene in water
WTO	toluene in water
WME	Methyl tert-butyl Ether (MTBE) in water
2DF	2,5-dimethylfuran in blood
VBZ	Benzene in blood
VEB	ethylbenzene in blood
VXY	m-/p-xylene in blood
VOX	o-xylene in blood
VTO	toluene in blood
VME	Methyl tert-butyl Ether (MTBE) in blood

Appendix G

Exposure Investigation Protocol

Biological and Environmental Monitoring for Exposure to Benzene and related petroleum constituents

Corpus Christi, Texas

Cost Recovery Number A835

March 2010

Prepared by:

Kenneth Orloff, PhD

Lourdes Rosales-Guevara, MD

Bruce Tierney, MD

ATSDR/DHAC/EISAB

Introduction

From October 2007 to March 2008, researchers from Texas A&M University (TAMU) collected blood and urine samples from residents living near "refinery row" in Corpus Christi, Texas. The stated purpose of the pilot project was to "develop appropriate protocols for biomarkers of exposure to petroleum hydrocarbons." TAMU reported that benzene concentrations in many of the blood samples were elevated. Some of the benzene concentrations were reportedly more than 100-times higher than the 95th percentile of the NHANES national data base (TAMU 2008).

TAMU was investigating a new protocol and was not following a validated analytical protocol. It is possible that the test results were artificially high because of the failure to purge VOCs that may have been present in Vacutainer^{TM} stoppers and other equipment used in sample collection, preparation, and analysis. Attempts to recalculate the results to correct for this potential source of error yielded values that were generally lower, but some values were still orders of magnitude above the NHANES 95th percentile value.

These results, if accurate, indicate that residents of the Hillcrest community are being exposed to large doses of benzene. A further investigation is warranted to determine if current exposures to benzene are elevated in residents of Hillcrest and other nearby communities.

Project Overview

A. Purpose

ATSDR will conduct biological monitoring and environmental monitoring for exposure to benzene and related aromatic hydrocarbons in residents living near refinery row. This biological and environmental monitoring will be conducted using validated, state-of-the-science analytical methodologies. The purpose of this investigation was to measure current levels of exposure to benzene and related petroleum VOCs in residents who live near refinery row.

B. Investigators and Collaborators

The Agency for Toxic Substance and Disease Registry (ATSDR), Division of Health Assessment and Consultation (DHAC), Exposure Investigations and Site Assessment Branch (EISAB) will be the lead for this Exposure Investigation (EI).

EISAB will:

(1) Work with the community to recruit participants for the EI

(2) Procure supplies for environmental monitoring

(3) Contract for local phlebotomists to draw blood samples

(4) Administer consent/assent forms and questionnaires

(5) Collect environmental and biological samples and ship them to laboratories for analysis

(6) Evaluate the analytical test results

(7) Notify the participants of their individual test results

(8) Write a report that summarizes the collective findings of the EI

National Center for Environmental Health (NCEH) will:

(1) Provide supplies for collecting blood and urine samples

(2) Analyze blood and urine samples for the chemicals of concern or their metabolites

The community will:

(3) Assist ATSDR in identifying and recruiting participants for the EI.

METHODS

A. Criteria for participation

ATSDR will work with the community to recruit residents with the highest potential exposures to benzene and related aromatic hydrocarbons from refinery row. Participation in this EI will be limited to people who currently live in the communities of Hillcrest or Dona Park, which are contiguous to refinery row. Residents of these communities could potentially be exposed to fugitive air emissions from the refineries, as well as to soil vapor intrusion from contaminated groundwater. The focus of the EI will be on adults who spend much of the day at home in these communities. Although adults are the focus of this EI, children who are willing to donate a blood sample can also be included. Participants from the previous TAMU pilot project are also eligible and are encouraged to participate.

Tobacco smoking is a significant source of benzene exposure. Participants will be questioned about their smoking habits, but smokers and their family members will not be excluded from this EI. Smokers will be identified by questionnaire information, as well as by the presence of 2,5-dimethylfuran, a component of tobacco smoke, in their blood samples (Ashley et al. 1996).

B. Recruiting participants

ATSDR staff will work with the community to select up to 100 people for testing in this EI. Recruitment efforts will include:

(4) ATSDR will meet with community leaders to discuss the proposed EI and solicit community input and support in contacting potential participants.

(5) ATSDR will develop a fact sheet for distribution to the public that describes the EI. The fact sheet will include a toll-free number that participants can call to schedule an appointment for testing.

(6) Two-person teams consisting of one community member and one ATSDR staff person will go door-to-door in Hillcrest and Dona Park to recruit participants for the EI.

C. Field activities

In the TAMU pilot project, the participants drove to a local health clinic where blood samples were collected. Driving in a vehicle on a highway is known to be a source of exposure to benzene in fuel and auto exhaust. Therefore, in this EI, ATSDR will collect blood samples from people in their homes. Benzene concentrations in blood samples collected from people in their homes will be more indicative of what people are exposed to in ambient air in their neighborhoods and inside their homes.

In order to maximize efficiency in collecting samples, ATSDR will give preference to households in which two or more people participate in the testing.

During the home visits, ATSDR will conduct the following activities:

First Visit:
- Administer consent/assent form (Appendix A)
- Distribute passive air sampling badges and explain how to use them
- Distribute urine collection cups
- Administer questionnaire

Second Visit (48 hours later):
- Collect exposed air sampling badges
- Collect urine samples
- Collect blood samples
- Complete questionnaire

Environmental testing

ATSDR will provide the participants with a passive air sampling device (3M^{TM} Organic Vapor Monitor 3500) for measuring VOC contaminants in the participant's personal air

space. It has been demonstrated that these devices are effective in measuring low concentrations of benzene and other volatile organic chemicals in air (Begerow et al. 1999, Chung et al. 1999).

The participants will be instructed to attach the device to their shirt collar and wear it throughout the day at all times. At night they should place it on a night table or other location near their bed. In the bathroom, it should be placed in an area where it will not get wet by splashing water, etc. The passive sampling device should be worn for 48 hours prior to having a blood sample collected. To protect anonymity, the sampling devices will be labeled with a coded identification number.

Biological testing

Urine

ATSDR will give each participant a urine collection cup. The participant will be instructed to collect a first-morning void or a random, spot urine sample of at least 30 ml. The participant should note the time of collection on the urine sample cup. The urine cup should be capped, sealed in a plastic bag, and placed in a refrigerator until collected by ATSDR. ATSDR will transfer a 5-ml aliquot of the urine into a cryovial and freeze it on dry ice. The urine samples will be kept frozen and shipped on dry ice. To protect anonymity, the samples will be labeled with a coded identification number.

Blood

A phlebotomist will collect a 10-ml blood sample in tubes that are specially prepared by NCEH for VOC analyses (Chambers et al. 2008). To protect anonymity, the tubes will be labeled with a coded identification number. After collection, ATSDR will hold the blood samples at refrigerator temperature (4° C) and ship them on ice packs.

Questionnaire

During the first home visit, ATSDR will begin to administer a questionnaire. The questionnaire is composed of questions to assess potential exposures to VOCs. The questions have previously been approved by the Office of Management and Budget. During the second home visit, questions that relate to activities during the previous two days will be completed.

D. Sample handling and shipping

The blood and urine samples will be shipped within 24 hours after collection. At the end of each day, ATSDR will package the biological samples on ice packs (blood) or dry ice (urine) and ship them by overnight delivery to the NCEH laboratory in Atlanta, Georgia for analysis.

ATSDR will place the environmental samples in sealed bags and ship them at ambient

temperature by overnight delivery to a contract laboratory for analyses (Bureau Veritas North America, Inc.; Novi, Michigan).

E. Lab processing and analysis

The blood and urine samples will be analyzed using published methodologies (Chambers et al., 2008; Ding et al., 2009) by the NCEH laboratory.

Blood samples will be analyzed for the following chemicals:

Benzene
Toluene
Ethylbenzene
ortho- xylene
meta- and para-xylene
Methyl t-butyl ether (MTBE)
2, 5-dimethylfuran

Urine samples will be analyzed for the following chemicals:

N-Acetyl-S-(phenyl)-L-cysteine (PMA , a metabolite of benzene)
Creatinine

The environmental samples will be analyzed by a contract laboratory that is certified by the American Industrial Hygiene Association (AIHA) to conduct these analyses using a National Institute for Occupational Safety and Health (NIOSH) approved protocol (reference). The samples will be analyzed for the following chemicals:

Benzene
Toluene
Ethylbenzene
ortho- xylene
meta- and para-xylene
Methyl t-butyl ether (MTBE)

F. Evaluation of data

Blood VOC results from adults will be evaluated using CDC's *Fourth National Report on Human Exposure to Environmental Chemicals* (CDC, 2009). Blood VOC results from children will be evaluated using data from two published studies that used the NCEH analytical methodology to measure blood VOC concentrations in children (Sexton et al. 2005, Sexton et al. 2006).

The presence of a detectable concentration of 2, 5-dimethylfuran in blood samples will be used as an indicator of exposure to tobacco smoke as described by Ashley et al. (1996). An NHANES comparison range for 2, 5-dimethylfuran is also available (CDC, 2009).

The concentration of PMA, a metabolite of benzene, in urine samples will be evaluated using the data reported by Ding et al. (2009).

The concentrations of VOC in personal air samples will be evaluated using ATSDR's Minimal Risk Levels (MRLs) and standard health assessment methodologies as described in ATSDR's Public Health Assessment Guidance Manual (Update) (ATSDR, 2005).

Benefits to the Community

The only risk to participants of this investigation is a chance of bruising from drawing a blood sample.

The potential benefit to the participants of this EI is that they will learn if they have had elevated exposures to benzene and other related aromatic hydrocarbons in petroleum products. If elevated exposures are detected, we will make recommendations for how to reduce exposures.

Notifying the Community of Test Results

ATSDR will send a letter to each participant of the EI to notify them of their test result. If any of the test results are elevated, ATSDR will make recommendations for how exposures may be reduced.

ATSDR will also provide contact information for a physician at ATSDR that the participants or their private medical care provider can call to discuss test results.

At the conclusion of this investigation, ATSDR will prepare a written report that presents the findings of the EI. This report will contain no personal identifiers to protect the anonymity of the participants. The report will be available to federal, state, and local environmental and public health agencies, as well as to the general public.

The consent form will request permission from the participants for ATSDR to share their test results with other federal and state health and environmental agencies.

Estimated Timeframe

ATSDR estimates that the field activities will begin in March 2010.

Sampling	2 weeks
Laboratory analysis	2 weeks
Data Evaluation	4 weeks
Notifying individuals of their test results	2 weeks
Writing report and clearance	8 weeks
Total:	18 weeks

References

Ashley, D.L., Bonin, M.A., Hamar, B., and McGeehin, M. Using the blood concentration of 2,5-dimethylfuran as a marker for smoking. Int Arch Occup Environ Health 68: 183-187 (1996).

Agency for Toxic Substances and Disease Registry. Public Health Assessment Guidance Manual (Update) (2005) http://www.atsdr.cdc.gov/HAC/PHAmanual/index.html

Begerow, J. Jermann, E., Keles, T., and Dunemann, L. Performance of two different types of passive samplers for the GC/ECD-FID determination of environmental VOC levels in air. Fresenius J Anal Chem 363: 399-403 (1999).

Centers for Disease Control. Fourth National Report on Human Exposure to Environmental Chemicals (2009) http://www.cdc.gov/exposurereport/

Chambers, D.M., Blount, B.C., McElprang D.O., et al. Picogram measurement of volatile n-alkanes (n-hexane through n-dodecane) in blood using solid phase microextraction to assess nonoccupational petroleum-based fuel exposure. Anal Chem 80: 4666-4674 (2008).

Chung, C-W, Morandi, M.T., Stock, T.H., and Ashfar, M. Evaluation of a passive sampler for volatile organic compounds at ppb concentrations, varying temperatures, and humidities with 24-h Exposures. 2. Sampler performance. Environ Sci Technol 33: 3366-3671 (1999).

Ding, Y.S., Blount, B.C., Valentin-Blasini, L. et al. Simultaneous determination of six mercapturic acid metabolites of volatile organic compounds in human urine. Chem. Res. Toxicol. 22: 1018-1025 (2009).

Sexton, K., Adgate, J.L., Church, T.R., et al. Children's exposure to volatile organic compounds as determined by longitudinal measurements in blood. Env. Health Perspect. 113(3): 342-349 (2005).

Sexton, K., Adgate, J.L., Fredrickson, A.L., et al. Using biologic markers in blood to assess exposure to multiple environmental chemicals for inner-city children 3-6 years old. Env. Health Perspect. 114(3): 453-459 (2006).

Texas A & M School of Rural Public Health, the Coastal Bend Health Education Center, and the Citizens for Environmental Justice. Report on Results of Nueces County Family Health Study. November 2008.

Appendix A

U.S. Department of Health and Human Services (DHHS)
Agency for Toxic Substances and Disease Registry (ATSDR)

Corpus Christi, Texas

Exposure Investigation (EI)

Adult Consent Form for Blood, Urine, and Personal Air Sampling

WHO ARE WE AND WHY ARE WE DOING THIS EXPOSURE INVESTIGATION (EI)?

We are from the Agency for Toxic Substances and Disease Registry (ATSDR), a sister agency to the Centers for Disease Control and Prevention (CDC). The purpose of the EI is to determine whether people who live in your neighborhood near the oil refineries have high levels of benzene and other petroleum-related volatile organic compounds (VOCs) such as toluene, ethyl benzene, and xylene (BTEX) in their bodies.

We are inviting you to have your blood, urine, and personal air tested for these chemicals. This testing will take place while you are in your home.

WHAT IS INVOLVED IN THIS EI?

In the blood test, a 10 ml sample of blood (less than 1 tablespoon) will be collected from a vein in your arm. This will take less than 10 minutes.

Urine testing. A person from ATSDR will tell you how to collect and store your urine sample. On the day of the test, you will collect your first morning urine or a random spot sample in a plastic cup we give you. You will put the cup in your refrigerator until ATSDR staff can pick it up. It should take 10 minutes or less for you to collect your urine sample.

The personal air samples collection. You will wear a personal air monitor badge for 48 hours prior to collecting your blood and urine sample.

Your blood, the urine and the air sample will be tested for benzene and other petroleum-related volatile organic compounds (VOCs). The blood sample will also be tested for 2, 5-dimethylfuran, a marker for tobacco smoking.

WHAT ARE THE **BENEFITS** FROM BEING IN THIS EI?

By being part of this EI, you will find out if you have high levels of benzene and other petroleum-related volatile organic compounds (VOCs) in your body. If elevated

exposures are detected, we will make recommendations for how you can reduce exposures.

WHAT ARE THE **RISK**S OF THIS EXPOSURE INVESTIGATION?

There may be some bruising in the bend in your elbow where the blood sample is collected.

There is no cost to you for this testing.

WHAT ABOUT MY PRIVACY?

We will protect your privacy as much as the law allows. We will give you an identification (ID) number. This number, not your name, will go on your blood, urine and personal air sample. We will not use your name in any report we write. We will keep a record of your name, address, and ID number so that we can send you the test result.

HOW WILL I GET MY TEST RESULTS

Your test results and an explanation of their significance will be mailed to you 6-8 weeks after testing. We will also give you a telephone number that you or your doctor can call to discuss your test results. ATSDR does not provide any follow-up medical care or evaluation.

WHAT IF I DON'T WANT TO DO THIS?

You are free to choose whether or not you want to be part of this testing. If you agree to be tested, you may change your mind and drop out at any time. You must sign this consent form to be tested.

WHO DO I CONTACT IF I HAVE QUESTIONS?

If you have any questions about this testing, you can ask us now. If you have questions later, you can call Dr. Kenneth Orloff at ATSDR at 770-488-0735.

VOLUNTARY CONSENT

I have read this form or it has been read to me. I have had a chance to ask questions about this testing and my questions have been answered. I agree to be part of this testing.

_____ _____

Participant's Signature Date

_____

Participant's Printed Name

Age _____ Gender _____

Address _____

_____

_____

Telephone number _____

May we share these test results with other Federal and State health and environmental agencies? YES _____ NO _____

Lab ID Number _____

I have read the consent form to the person named above. He/she has asked questions about the investigation and had the questions answered.

_____
Signature of person administering consent form

U.S. Department of Health and Human Services (DHHS)
Agency for Toxic Substances and Disease Registry (ATSDR)

Corpus Christi, Texas

Exposure Investigation (EI)

Parental Consent Form for Blood, Urine, and Personal Air Sampling for Children Less Than 10 Years of Age

WHO ARE WE AND WHY ARE WE DOING THIS EXPOSURE INVESTIGATION (EI)?

We are from the Agency for Toxic Substances and Disease Registry (ATSDR), a sister agency to the Centers for Disease Control and Prevention (CDC). The purpose of the EI is to determine whether people who live in your neighborhood near the oil refineries have high levels of benzene and other petroleum-related volatile organic compounds (VOCs) such as toluene, ethyl benzene, and xylene (BTEX) in their bodies.

We are inviting your child/ward to have his/her blood, urine and personal air tested for these chemicals. This testing will take place while your child/ward is in his/her home.

WHAT IS INVOLVED IN THIS EI?

In the blood test, a 10 ml sample of blood (less than 1 tablespoon) of your child/ward will be collected from a vein in your child/ward's arm. This will take 10 minutes.

Urine testing. A person from ATSDR will tell you how to help collect and store your child/ward's urine sample. On the day of the test, your child/ward will collect his/ her first morning urine or a random spot sample in a plastic cup we give you. You will put your child/ward's cup in your refrigerator until ATSDR staff can pick it up. It should take 10 minutes or less for you to help your child/ward collect his/ her urine sample.

The personal air samples collection. Your child/ward will wear personal air monitor badge for 48 hours prior to collecting his/her blood and urine sample.

The blood, the urine and the air sample will be tested for benzene and other petroleum-related volatile organic compounds (VOCs). The blood sample will also be tested for 2, 5-dimethylfuran, a marker for tobacco smoking.

WHAT ARE THE **BENEFITS** FROM BEING IN THIS EXPOSURE INVESTIGATION?

By being part of this EI, you will find out if your child/ward has high levels of benzene and other petroleum-related volatile organic compounds (VOCs) in his/her body. If elevated exposures are detected, we will make recommendations for how you can reduce exposures.

WHAT ARE THE **RISKS** OF THIS EXPOSURE INVESTIGATION?

There may be some bruising in the bend in your child/ward's elbow where the blood sample is collected.

There is no cost to you for the testing of your child/ward.
WHAT ABOUT MY CHILD/WARD PRIVACY?

We will protect your child/ward privacy as much as the law allows. We will give your child/ward an identification (ID) number. This number, not your child/ward's name, will go on the blood, urine and personal air sample. We will not use your child/ward's name in any report we write. We will keep a record of your child/ward's name, address, and ID number so that we can send you the test result.

HOW WILL I GET MY CHILD'S/WARD'S TEST RESULTS

Your child's test results and an explanation of their significance will be mailed to you 6-8 weeks after testing. We will also give you a telephone number that you or your child's doctor can call to discuss the test results. ATSDR does not provide any follow-up medical care or evaluation.

WHO DO I CONTACT IF I HAVE QUESTIONS?

If you have any questions about this testing, you can ask us now. If you have questions later, you can call Dr. Kenneth Orloff at ATSDR at 770-488-0735.

VOLUNTARY CONSENT

I agree to allow my child/ward to be tested. I and my child/ward have been given a chance to ask questions and feel that all questions have been answered. I know that being in this testing is our choice. I know that after choosing to be in this testing, my child/ward may leave it at any time.

SIGNATURE

I give permission for my child/ward to be tested.

_____

Printed Name of Child

_____ _____

Signature of Parent/Guardian Date

_____

Printed Name or Parent/Guardian

Age of child _____ Gender of child_____

Address of child:

_____

_____

_____

Telephone number _____

May we share these test results with other Federal and State health and environmental agencies? YES _____ NO _____

Lab ID Number _____

I have read the consent form to the person named above. He/she has asked questions about the investigation and had the questions answered.

_____

Signature of person administering consent form

U.S. Department of Health and Human Services (DHHS)
Agency for Toxic Substances and Disease Registry (ATSDR)

Corpus Christi, Texas Exposure Investigation (EI)

Assent Form for Blood, Urine, and Personal Air Sampling for Children 10-17 Years of Age

WHO ARE WE AND WHY ARE WE DOING THIS TESTING

We are from the Agency for Toxic Substances and Disease Registry (ATSDR). The purpose of the EI is to determine whether people who live in your neighborhood near the oil refineries have high levels of benzene and other petroleum-related volatile organic compounds (VOCs) such as toluene, ethyl benzene, and xylene (BTEX) in their bodies.

We are inviting you to have your blood, urine and personal air tested for these chemicals This testing will take place while you are in your home.

WHAT IS INVOLVED IN THIS EI?

In the blood test, a 10 ml sample of blood (less than 1 tablespoon) will be collected from a vein in your arm. This will take 10 minutes.

Urine testing. A person from ATSDR will tell you how to collect and store your urine sample. On the day of the test, you will collect your first morning urine or a random spot sample in a plastic cup we give you. You will put the cup in the refrigerator until ATSDR staff can pick it up. It should take 10 minutes or less for you to collect your urine sample.

The personal air samples collection. You will wear a personal air monitor badge for 48 hours prior to collecting your blood and urine sample.

The blood, the urine and the air sample will be tested for benzene and other petroleum-related volatile organic compounds (VOCs). The blood sample will also be tested for 2, 5-dimethylfuran, a marker for tobacco smoking.

WHAT ARE THE **BENEFITS** FROM BEING IN THIS EXPOSURE INVESTIGATION?

By being part of this EI, you will find out if you have high levels of benzene and other petroleum-related volatile organic compounds (VOCs) in your body. If elevated exposures are detected, we will make recommendations for how you can reduce exposures.

WHAT ARE THE **RISKS** OF THIS EXPOSURE INVESTIGATION?

There may be some bruising in the bend in your elbow where the blood sample is collected.

There is no cost to you for this testing.

WHAT ABOUT MY PRIVACY?

We will protect your privacy as much as the law allows. We will give you an identification (ID) number. This number, not your name, will go on your blood, urine and personal air sample. We will not use your name in any report we write. We will keep a record of your name, address, and ID number so that we can send you the test result.

HOW WILL I GET MY CHILD'S/WARD'S TEST RESULTS

Your test results and an explanation of their significance will be mailed to your parents 6-8 weeks after testing. We will also give your parents a telephone number that they or your doctor can call to discuss the test results. ATSDR does not provide any follow-up medical care or evaluation.

ASSENT

Your parents/guardian said it is all right for you to have this test. You don't have to if you don't want to.

WHAT IF I HAVE QUESTIONS?

If you have questions, you can ask us now. You can talk with your parents if you want. If you have questions later, ask your parent. They can call us for answers.

SIGNATURE
I have read this form or it has been read to me. I have had a chance to ask questions about this testing and my questions have been answered. I agree to be part of this testing.

_____ _____
Signature of Minor Date

_____
Printed Name of Minor

_____
Signature of Parent

Age of Participant _____ Gender of Participant_____

Address: _____

_____

_____

Telephone number _____

May we share these test results with other Federal and State health and environmental agencies? YES _____ NO _____

Lab ID Number _____

I have read the consent form to the person named above. He/she has asked questions about the investigation and had the questions answered.

_____
Signature of person administering consent form

Appendix H

Peer Review Comment Form: Exposure Investigation
Reviewer #1

Guide to Reviewers:
The objective of peer review conducted by the Office of Science, NCEH/ATSDR is to ensure the highest quality of science for NCEH/ATSDR studies and results of research; therefore, your comments should be provided with this goal in mind. The questions to be addressed for NCEH/ATSDR are broadly based so that each reviewer may have wide latitude in providing his/her comments. The preferred format for responses is to insert your comments below each question in this WORD document, then to return the completed form as an e-mail attachment. Please do not forget to check the appropriate boxes.

Please note that your unaltered comments will be sent to the investigator for a response. You should receive a copy of the response to the peer reviewer comments when they are available.

1. Are the exposure investigation's objectives clearly stated and appropriate?
   Yes (X) No ( ) Unsure ( )

   The objective to test whether the results of the previous investigation that had insufficient QA/QC is a reasonable objective and is clearly stated.

2. Were the methods and analysis plan appropriate for the exposure investigation's objectives?
   Yes (X) No ( ) Unsure ( )

   The measurement methods are state of the science for the most part (though the OVM MDLs are a bit high). My major scientific criticism of the study design is that it only looks at the exposure patterns for 3 days. While this is reasonable for cost/logistical purposes, it may not be completely representative given the potential impacts of variability in source emissions and meteorology. It would be useful for the reader to know what the duration of sampling was for the TAMU pilot study as well, and to state explicitly in the abstract that a 3 day sampling period was used. In relating the advantages of this study verses the previous study the report should explicitly state and compare the two study designs, with a focus on the number of calendar days of sampling, duration of sampling, and the number of sampled subjects. State clearly that 90 people were sampled for blood and urine and OVM, and 12 water samples were taken and analyzed.

3. Was the existence of potential pathways of human exposure appropriately considered in designing the strategy for collection of environmental and human samples?
   Yes (X) No ( ) Unsure ( )

Air and water were the main pathways considered and air is clearly the main pathway. This is reasonable based on the existing literature, which clearly shows that the main sources of BTEX exposure is inhalation in most cases.

4. Were the samples collected using appropriate methods and QA/QC procedures?
   Yes (X) No ( ) Unsure ( )
5. Were the samples analyzed using appropriate analytical methods? Were good laboratory practices, including quality assurance and quality control procedures for laboratory analyses, used where appropriate?
   Yes (X) No ( ) Unsure ( )

   Response to 4 and 5: Sampling and Analysis Methods are clear, state of the science, and have appropriate QA/QC methods, such as field blanks. There's little mention of split or spiked samples. QA/QC on the CDC lab materials is a lot clearer than for the OVMs. OVM performance is OK, but MDLs are a bit high relative to a number of other studies that have been done using this method (See work by Sexton et al., Stock and Morandi, Weisel's RIOPA papers, etc.).

6. Were the data analyzed in such a way to address appropriately the objectives of the exposure investigation? Were the exposure data collected during this exposure investigation correctly interpreted? Were the comparison data appropriate?
   Yes (X) No ( ) Unsure ( )

Given the sample size the objectives and analysis methods are appropriate: non parametric tests are reasonable given the expected underlying distributions. You should provide more distributional information, as arithmetic means are probably not the right measure of central tendency for these likely log normally distributed distributions: use Geoetric Means/GSD and/or median's.

7. Are the exposure investigation results presented and interpreted appropriately and completely? Did this exposure investigation accomplish its stated objectives?
   Yes (X) No ( ) Unsure ( )

   See above on Stats. Stated objectives accomplished.

8. Are scientific uncertainties clearly identified and characterized?
   Yes (FOR THE MOST PART) (X) No ( ) Unsure ( )

Major uncertainties have to do with the sample size and duration. The selection of 90 subjects from ~50 households leads to some autocorrelation in the data, but the benefit of the larger sample size is a reasonable payoff. It is hard to argue that the levels observed are representative of longer term exposure given that samples were only collected on 3 calendar days.

9. Were the limitations of the exposure investigation adequately noted?

Yes ( ) No (X) Unsure ( )

This could be strengthed, as noted above. Limited number of days, limited number of people. Note the size of the population relative to NHANES and other studies (e.g., Sexton et al., many others)

10. Are the conclusions and recommendations supported by the findings of the exposure investigation? Are the conclusions and recommendations appropriate and complete?
Yes (X) No ( ) Unsure ( )

Conclusions can be strengthened:
#1. The TAMU results are uncertain and not supported by rigorous QA/QC that calls its results into question.
#2 Note the there are other biomonitoring and OVM studies of general and special populations that indicate the same thing. Some of these, like Wallace's early work and RIOPA purposely sampled communities thought to be highly exposed only to show that personal exposure is dominated by nearby sources. Levels in this population do not appear to be unusual.
#7 Note that its more complicated than this indicates in the first sentence: there are no health-based standards for any of these in blood or urine.

11. Are the references appropriate and relevant to the exposure investigation? If not, provide additional reference materials/information.
Yes (X) No ( ) Unsure ( )

There's a bigger VOC literature on some issues that could be cited: while NHANES is a good reference population, the literature on the activities that lead to high end exposure (e.g., pumping gas) is not cited.

12. Are there any other comments about the exposure investigation that you would like to make?

Citation of some of the basic work in this area is a bit thin: for example its not hard to find the cite that shows the impact of smoking of personal benzene exposure.

13. Are there any comments on ATSDR's peer review process?

No.

RECOMMENDATION

What is your overall recommendation on this exposure investigation? Please select the appropriate category below:

Recommend (XXX).

Recommend with Required Changes ( ).

List recommended changes:

Not Recommended ( ).
List reasons for not recommending:

Response to Comments from Peer Reviewer #1

(2) The EI took place over a 4-day period. ATSDR acknowledges that the 4-day period of the investigation may not be representative of past or future exposures in the community. Additional text was added to the limitations section to highlight this point. The details and study design of the TAMU study have not been publically released, so it is not possible to compare the two investigations.

(5) The OVM samples were analyzed using a standardized, NIOSH approved protocol with QA/QC procedures described in the cited reference. Spiked samples were within acceptable limits and no contaminants were detected in blank samples.

(6) Geometric mean concentrations and confidence intervals were added to the report when the data allowed them to be calculated. Additional statistical analyses were included to provide a more complete analysis of the data.

(8) ATSDR acknowledges that the findings of this EI may not be representative of long term exposures in the community. Furthermore, the EI participants were a biased sample: ATSDR intentionally tried to recruit participants who lived close to refinery row and who were at home much of the time. Thus, these participants could have higher exposures to ambient air contaminants than the community-at-large.

(9) The limitations section of the report was revised to more clearly articulate the limitations of the EI.

(10#1) As discussed in the Introduction, the TAMU test results were one factor that prompted ATSDR to conduct this EI. However, it was not the purpose of this EI report to critique the TAMU test results.

(10#2) ATSDR added references to the report for some of these other studies. ATSDR used NHANES data as our comparison population because both studies used the same analytical methodology, and NHANES is representative of national exposures.

(10#7) This conclusion was deleted.

(11) Additional references added, including the effect of pumping gasoline.

(12) Additional references added, including the effect of smoking.

Peer Review Comment Form: Exposure Investigation Reviewer #2

Guide to Reviewers:
The objective of peer review conducted by the Office of Science, NCEH/ATSDR is to ensure the highest quality of science for NCEH/ATSDR studies and results of research; therefore, your comments should be provided with this goal in mind. The questions to be addressed for NCEH/ATSDR are broadly based so that each reviewer may have wide latitude in providing his/her comments. The preferred format for responses is to insert your comments below each question in this WORD document, then to return the completed form as an e-mail attachment. Please do not forget to check the appropriate boxes.

Please note that your unaltered comments will be sent to the investigator for a response. You should receive a copy of the response to the peer reviewer comments when they are available.

1. Are the exposure investigation's objectives clearly stated and appropriate?
   Yes (x) No ( ) Unsure ( )
   Why? Generally ok but better to say that objective was to measure current levels of exposure using personal air, urine and blood samples collected from residents who live near refinery row. Not "in residents"

   Response: *Text was revised as suggested.*

2. Were the methods and analysis plan appropriate for the exposure investigation's objectives?
   Yes ( ) No ( ) Unsure (x)
   Why? In general, most of the methods and analysis plan were appropriate although the plan could have been strengthened by (1) sampling more individuals and homes (and not sampling two individuals within a home although the logistical factors are appreciated); (2) specifying criteria for the locations of the homes within the two communities, e.g., within a specified distance of the refineries; (3) selecting periods when meteorological conditions were more favorable for exposure; and (4) accounting for the differences in the age of the cohorts, namely, the participants age (range = 7 – 91 years, and average = 56 years) differs from the NHANES' participants (range = 20 – 59 years).

   Response: *(1) ATSDR was limited by resources to test approximately 100 people. (2) During recruitment, ATSDR told the community that we wanted to test people who lived close to Refinery Row. However, there were no strict geographical limitations, other than the participants had to live in communities of Hillcrest or Dona Park. The participants were self-selected. (3) The EI had to be planned months in advance, and it was not possible to be on standby, waiting for*

meteorological conditions to be "favorable." Nevertheless, during the two days of the blood draws, the wind blew predominantly from the communities toward the refineries on day 1, and from the refineries toward the communities on day 2, allowing for a comparison of contrasting wind direction. (4) While we agree with the reviewer that people of different ages could have different VOC exposure, age was NOT found to be a statistically significant variable in a multiple regression analysis we conducted. Additionally, studies of VOC exposure of children and adults tend to find similar levels of exposure once variables such as smoking are included (Sexton et al 2006; Lin et al.). Furthermore, one of our objectives was to follow-up on the TAMU results that indicated Hillcrest residents had high ppb range benzene levels in their blood. Thus, we tried to sample people who lived in close proximity to the refineries, the potential sources of the exposure.

Sexton K, Adgate JL, Fredrickson AL, Ryan AD, Needham LL, Ashley DL. Using biologic markers in blood to assess exposure to multiple environmental chemicals for inner-city children 3-6 years of age. Environ Health Perspect. 2006 Mar;114(3):453-9.

Lin, YS, Egeghy, PP, and Rappaport, SM. Relationships between levels of volatile organic compounds in air and blood from the general population. J Exp. Science and Env. Epidem. 18: 421-429 (2008).

On the last point, it is clear that time activity patterns of both younger and older individuals differ from say working adults. The analysis may not have sufficient sample size if only adults 20-59 years of age are included. But this should be examined.

Response*: ATSDR attempted to recruit people who lived closest to refinery row and were home much of the time. Hence, we attempted to recruit a biased sample of people who were most likely to be exposed to potential emissions from refinery row – i.e., a worst case scenario. ATSDR made no attempt to sample a representative cross-section of the community. If refinery row is a significant source of exposure, the people who work or go to school outside the community would be expected to have lower exposures than people who remain in the community much of the day.*

3. Was the existence of potential pathways of human exposure appropriately considered in designing the strategy for collection of environmental and human samples?
   Yes ( ) No ( ) Unsure (x)
   Why? Inhalation is the principal exposure pathway for refinery-related emissions; water is a potential secondary pathway. It is suggested that soil vapor intrusion might be a pathway, but no specific measurement is provided that isolates this pathway.

Response: *The EI was intended to look at <u>total</u> exposure, regardless of exposure pathway. We assumed the majority of the exposure to VOCs would be through inhalation, but we made no attempt to individually evaluate possible exposure pathways. VOCs from soil vapor intrusion into homes, had it occurred, would have contributed to indoor air VOCs.*

4. Were the samples collected using appropriate methods and QA/QC procedures?
   Yes (x) No ( ) Unsure ( )
   Why? Yes, except as noted above in 4.

5. Were the samples analyzed using appropriate analytical methods? Were good laboratory practices, including quality assurance and quality control procedures for laboratory analyses, used where appropriate?
   Yes (x) No ( ) Unsure ( )
   Why?

6. Were the data analyzed in such a way to address appropriately the objectives of the exposure investigation? Were the exposure data collected during this exposure investigation correctly interpreted? Were the comparison data appropriate?
   Yes ( ) No (x) Unsure ( )
   Why? There are a number of analyses and presentations that are needed to make this EI more complete and valid. This response also has to deal with the presentation question (#7). These are listed below (page/line).

   P5/L1: should define point and fugitive, also note flares; also define vapor intrusion

   Response: *Added flares as potential exposure source*.

   P5/L4: Tobacco smoking should include exposure to ETS; also, ETS is a source of benzene "and other VOCs"

   Response: *Text added as suggested.*

   P5/L30: Taking two individuals from each home, while helping to increase efficiency of sampling, represents a clustered sample design, requiring some further statistical analyses since measurements from homes are expected to be correlated. At a minimum, should correlation between homes and determine whether samples can be considered to be dependent. If not, which is expected, then the "effective" sample size is reduced. Even so, 50 separate household is estimated to be a sufficient number.

   Response: *ATSDR agrees that there may be some clustering of results in homes with multiple residents, so there could be fewer than 90 independent samples. However, it is not ATSDR's contention that the EI participants*

were representative of the community-at-large. Recruitment for the EI focused on people who lived near refinery row and were home much of the day. Hence, the EI population was biased with people who might have higher than typical exposures. Therefore, we emphasize that these results are specific for the EI participants, and we did not attempt to use these data to draw statistical inferences for the rest of the community.

A map showing locations of sampled homes (highlighting individual homes) is useful to show coverage. Also, the map could show households that had water sampling.

Response: *Confidentiality requirements prevent ATSDR from revealing the location of the homes tested.*

P8/L40: Clearly one of the most significant limitations is that sampling was conducted on only 3 days, only 1 of which had winds predominantly from the refineries. Several additions to the report would aid interpretation of data.

a) Present annual (long-term) wind rose, which would help to judge how representative the 3-day period was. Optionally, but even better, since this is a coastal community, breakdown by time of day, to show sea breeze, shore breeze, etc, and also by season, which may indicate which periods of day and year are most likely to be problematic
b) Show traces of wind direction and wind speed over 3 day period
c) Show traces of VOC (and other) monitoring data at Oak Park monitoring station. This is important in showing possibility of contributions from refinery.
d) The Oak Park monitoring data could be analyzed to show when refinery contributions are most significant

Response: *ATSDR acknowledges that meteorological conditions, including wind direction, could affect test results. ATSDR clearly states that the test results apply only to the time period of the EI. It is virtually impossible to predict in advance when meteorological conditions "are most likely to be problematic."*

The reviewer misinterprets the purpose of this EI. It was beyond the scope of this EI to conduct wind trace analysis to try to identify possible sources of ambient air contaminants, or to correlate ambient air monitoring data with refinery activities.

P9/L30 I believe that the stats given for Oak Parks station are hourly (clarify). Should provide total sample size (n); The EPA 2010 reference is 24-hr, thus the comparison of the percentiles is not appropriate. Also, discuss

the relevance of the EPA data, which are taken mostly in highly urbanized areas, as compared to refineries or "background" areas.

Response: *Text revised and hourly air monitoring data from Oak Park Station provided in an appendix.*

P9/L30 Prefer tables comparing material given in text with this Oak Creek (and other) data.

P11/Tables 2-3 and related discussion. The NHANES data still provides the best comparison to blood and personal air, however, there are many limitations which require some elaboration.

a) How was the NHANES data smoking status determined? Cotinine? Questionnaire. If should be noted that in the Lin et al. study, smoking status was determined by serum cotinine (there was no 2,5-DMF data in NHANES 1999/2000). In this EI, smoking status was determined by blood 2,5-DMF. The use of 2,5-DMF may increase differences.

Response: *Scientists have validated numerous methods for identifying cigarette smoke exposure, including serum cotinine and blood 2,5-dimethylfuran. Serum cotinine and blood 2,5-dimethylfuran concentrations are correlated. However, the toxicokinetics of benzene in the human body associated with tobacco smoke exposure more closely resemble those of 2,5-dimethylfuran than cotinine, so we used 2,5-dimethylfuran levels in blood to assign smoking status to both the EI data set and the reference population (NHANES 2003-2004). The NHANES 1999-2000 blood VOC data were not used in this report as reviewer 2 states. Thus, different biomarkers were <u>not</u> used to assess tobacco smoke exposure in the EI compared with our analysis of the NHANES 2003-2004 reference data. We have added clarifying text to the footnotes of Tables 4 and 5.*

b) The 1999-2000 data are now 10 years old. Our recent analysis (in progress, I can send you a manuscript shortly) indicates that substantial drops in VOC exposure occurred between 1999/2000 and 2003/2004 HNANES data for blood. While the EI uses the latest data for blood, as is appropriate, the airborne VOC data available from the 1999/2000 NHANES dataset is now obsolete as it reflects "older" data. No national datasets are available, but based on indoor and ambient (and limited personal monitoring), I would expect personal air samples to be more on the order of 1 – 2 ug/m3 for benzene for non smokers. In any event, the age of the NHANES personal air dataset and the downward trends needs discussion.

Response: *Comparisons made with the blood VOC data and with the personal air data were done separately with the most recent corresponding NHANES data available, which we prefer to make as opposed to not making any comparison at all. Thus, the blood VOC data was compared to NHANES 2003-2004, and the personal air data was compared with NHANES 1999-2000. Reviewer #2's comment regarding the drop in blood benzene from 1999 to 2004 is well known, as exposure to ETS and benzene in fuel has decreased over that period with recent changes in environmental public health policies. Changes in current national estimates of personal air levels based on Reviewer #2's estimations are very small in comparison to levels that would be estimated from the TAMU study. Estimating what those levels might be now is conjecture and is outside the scope of this EI. However, the text was revised to note that VOC air concentrations may have decreased since 2000.*

c) Tables 1 & 2 could be combined and additional statistics should be added. Since only 50 homes were sampled, the 95th percentile value represents the 2nd or maybe 3rd highest value. This is not a robust statistic. I would suggest also showing the 90th percentile, since this will be a little more robust given the number of samples collected.

Response: *In its EIs, ATSDR has traditionally reported results back to the individual participants in comparison to the 95th percentile of NHANES as a reference value. This is very useful information to the individuals who were tested. ATSDR recognizes that because of the limited number of people tested in the EI, the number or percent of people above the 95th percentile is not a robust value. Furthermore, it is not ATSDR's contention that the EI participants were representative of the community-at-large. Recruitment for the EI focused on people who lived near refinery row and were home much of the day. Hence, the EI population was biased with people living closest to the refineries. Therefore, we emphasize that these results are specific for the EI participants, and we did not attempt to use these data to draw statistical inferences for the rest of the community.*

d) An appendix should present all of the data collected.

Response: *ATSDR will provide the EI data upon request.*

e) Reference values at other percentiles from the NHANES personal air data are given in several other papers, e.g., Jia et al., "Distributions of personal VOC exposures: A population-based

analysis," Environment International 34 (2008) 922–931. Note that there were slightly different criteria for excluding participants in NHANES 1999/2000, Jia et al (n = 665) and Symanski et al. (n = 644), which resulted in slightly different statistics, e.g., the 95th percentile concentrations, especially for m,p-xylene (69.8 μg m^{-3} in Jia et al. study vs. 76.3 μg m^{-3} in Symanski et al.). This difference may slightly influence the results of number of samples greater than the NHANES 95th percentile.
It should also be noted that MTBE concentrations were available in Jia et al.

Response: *There is no compelling basis for using the slightly different reference values of Jia et al. over those of Symanski et al., given that they were both derived from the same NHANES data set.*

The Jia et al. reference for the MTBE 95th percentile was added to the report.

f) A statistical comparison of differences in personal air levels would be helpful.

Response: *The geometric mean concentrations and their confidence intervals were provided where feasible.*

P12/L10 The first paragraph discussing blood and also Table 4, discussing detection frequencies, does not constitute a meaningful nor robust analysis, since detection frequencies are really a function of detection limits, and do not show sensitivity to levels found. The NHANES detection frequencies in Table 4 do not appear to be correct, e.g., detection frequencies were 58.5, 67.5, 98.4, 37.0, 95.0, and 26.1% from benzene to 2,5-DMF, based on the documentation of NHANES 2003/2004.

Response: *The NHANES detection frequencies we reported in Table 3 are taken from the actual data file and weighted and are correct, whereas Reviewer #2 derived detection frequencies from the "Docs" and did not adjust for sample design as recommended by the National Center for Health Statistics (NCHS). The frequencies reported in the "Docs" are sometimes in error and it is important for users of the NHANES data to be aware that NCHS handles many millions of results and that it is a prime responsibility of the researcher to check over the data even down to the level of a single result, as human error is possible.*

Frequency analysis is a meaningful and widely accepted method for comparing categorical data. The majority of the blood samples from non-smoking EI participants did not contain detectable concentrations of benzene or most of the other BTEX compounds; this causes the central

tendency values of exposure levels to be ambiguous. Furthermore, imputing data below the LOD is not practiced by NCHS as assumptions would need to be validated, which is again outside the scope of this EI. Thus, the primary publication of NHANES exposure data (National Exposure Report) by NCHS does not present means for analytes with detection frequencies < 60%. The only valid comparison that can be made is with detection frequencies and ranges (Table 3) to provide proper perspective and point of reference for benzene exposure in the EI population.

The same detection limits were used for both the EI sample analysis and the NHANES 03-04 reference population analysis (e.g. benzene detection limit of 0.024 ng/mL). The one exception is that the o-xylene method used in the EI was more sensitive than the method used for the NHANES 03-04 analysis, and thus would over-estimate percent of samples > LOD. Thus the finding that the o-xylene detection rate is lower in the EI compared with NHANES provides further evidence that the EI population did not have elevated exposure to petroleum-related VOCs compared with the reference population.

P13/Table 5 Several comments on the blood analysis

a) This table seems to have the arithmetic mean. Should present geometric mean (like Table 2) - but must also make comparable to reference data.

Response: *These were revised to the geometric means.*

b) Table omits mean of NHANES data. So comparison of means is not provided, which is the most important difference.

Response: *Geometric means for the EI and NHANES data were provided when the data permitted – i.e., when > 60 percent of the samples were above the LOD.*

b) Suggest combining Tables 5 and 6, and presenting additional statistics.

Response: *Tobacco smoke exposure is associated with increased VOC levels in blood samples. Therefore, it is preferable to present both NHANES and the EI data categorized by smoking status. Geometric means and confidence intervals were added to the tables.*

c) Number exceeding the 95th percentile level not too meaningful, given small sample size.

Response: *See response to page11/Tables 2-3/c.*

d) A statistical comparison of differences in blood levels would be helpful.

Response: *ATSDR provided the geometric means, where feasible, and the confidence intervals for further statistical comparisons.*

e) The analysis should better address concentrations below the limit of detection in the blood VOC data. This may influence the means of VOCs with low detection frequencies.

Response: *The actual concentrations of VOCs in samples below the LOD are unknown. Thus, we substitute values below the LOD as LOD/square root of 2. However, if the number of observations below LOD is ≥ 40%, the estimates of geometric means will be unstable. The point of the study was to examine whether the EI population had elevated exposures to petroleum VOCs. Comparison of the EI population with NHANES data provided proper perspective and point of reference for the blood VOC levels we measured. The study was not designed to explore minor variations in blood VOC levels below the parts-per-trillion detection limits.*

f) The analysis is unclear how smoking status in the NHANES dataset was determined. Both cotinine and 2,5-DMF concentrations were available in NHANES 2003/2004. Which one was used to determine smoking status of the NHANES participants in this EI?

Response: *This comment was previous made as Comment 6.8. The response given was as follows: "Scientists have validated numerous methods for identifying cigarette smoke exposure, including serum cotinine and blood 2,5-dimethylfuran. Serum cotinine and blood 2,5-dimethylfuran concentrations are correlated. However, the toxicokinetics of benzene in the human body associated with tobacco smoke exposure more closely resemble those of 2,5-dimethylfuran than cotinine, so we used 2,5-dimethylfuran levels in blood to assign smoking status to both the EI data set and the reference population (NHANES 2003-2004). The NHANES 1999-2000 blood VOC data were not used in this report as reviewer 2 states. Thus, different biomarkers were <u>not</u> used to assess tobacco smoke exposure in the EI compared with our analysis of the NHANES 2003-2004 reference data. We have added clarifying text to the footnotes of Tables 4 and 5."*

P14/Discussion The discussion should include a description of other refinery emissions, e.g., lighter compound not measured, upsets, etc., and possibly describe their health significance, and why these were not tested

Response: *The reviewer misinterprets the purpose of the EI. It was beyond the scope of this EI to conduct a comprehensive assessment of chemicals found in petroleum products and their health significance. Benzene was the focus of this EI because it is one of the constituents of petroleum products with the greatest relative toxicity.*

P15/L1-8 I suggest eliminating the discussion of the data prior to 2000 (and possibly even later data) as these levels are definitely too high. More recent discussions of benzene and other VOC levels indoors and outdoors are provided by Jia et al.
"VOCs in industrial, urban and suburban neighborhoods, Part 1: Indoor and outdoor concentrations, variation, and risk drivers," Atmospheric Environment 42 (2008) 2083–2100. Note also that this paper reviews ambient and indoor studies after 2000.

Response: *Additional references and more recent data have been provided, as suggested.*

P.15/L10-20 There is no discussion of cancer risks in this EI, although there is discussion of ATSDR MRL levels. I don't understand this dichotomy. Certainly, 2 or 3 days of monitoring represent a snapshot of exposure information, and there are limitations for estimating either short- or long-term health implications. This may be the point of the forthcoming public health assessment, but it seems unbalanced in the present write-up.

Response*: In the report, ATSDR noted that the results of this EI are not representative of past or long-term exposures. Cancer risks are dependent on long-term/lifetime exposures to carcinogens. Therefore, it would be inappropriate to estimate cancer risk based on this limited EI data. ATSDR's forthcoming Public Health Assessment will address cancer risks associated with long-term ambient air monitoring data from refinery row.*

If cancer risks are to be discussed, then the range presented by EPA's IRIS database should be discussed. Data from the permanent site monitor could be used.

Response: *This report evaluates the data gathered during the EI. It is beyond the scope of this report to evaluate data from ambient air*

monitors in the area. ATSDR's forthcoming Public Health Assessment will address these data.

I'd suggest a table presenting the different concentrations/averaging times for each VOC to discuss the health aspects.

Response: *The purpose of this EI was to assess exposure. Assessment of health impacts was outside the scope of this investigation.*

P15/L2 On the discussion of MTBE in water, the discussion should make clear that 3000 ug/L is a 10 day advisory; that lower levels are used for chronic exposure; and that California and other states have levels that are far lower. Also, this very low level found looks like a blank contamination issue, or a MDL issue. What was the MDL for water?

Response*: The 3,000 µg/L value is not a 10-day advisory. It is based on ATSDR's intermediate MRL, which applies to exposure periods of > 14 days to < 365 days. In response to this comment, the text was revised to include a comparison to EPA's drinking water advisory for MTBE in lieu of the intermediate MRL. The LOD (MDL) for MTBE in water is provided on page 11 of the report.*

Presumably all of the water comes from the same WTP; this should be discussed.

Response: *Clarification added.*

P15/L37 The geometric mean concentration of MTBE in personal airborne samples was 3 times higher in the EI than NHANES. It was not just "slightly" higher.

Response*: Text revised.*

P18/Figure 2: Possibly omit the 3 outliers and reconsider the correlation. Additionally, consider separating by smoking status. Note that in Lin et al., the association between blood and airborne benzene was quite different after adjusting for smoking status.

Response: *The blood:air correlation for smokers was calculated separately from the total EI population. The Lin reference for the different correlation between smokers and nonsmokers was cited.*

P18/L15 The text discusses the 90th percentile of blood benzene - which is not presented in this EI

Response: *The text is simply making the factual point that adults have higher blood concentrations than children at the 90th and 95th percentiles because of cigarette smokers in the adult population. No comparisons are made to the 90th percentile.*

P18/L25 Yes, I agree that the 95th percentile is arbitrary, so why was it used in an investigation that had a limited sample size? In particular, since there were only 90 participants, but only 45 homes, the 95th percentile is the top 2nd or 3rd measurement!

Response: *The issue of the preciseness of the 95th percentile has been previously discussed (P11/Tables 2-3/c). The point of the text is not to imply we can predict the precise number of people who would be above the 95th percentile. Rather it makes the point that at least some of the EI participants would be expected to exceed the NHANES 95th percentile if the two populations had similar exposures.*

P19/L10 This is a good attempt to look at levels on day 1 vs. day 2. The description should describe the sample size on each day; should consider the location of the participant homes; and information on the smoking status and day of sampling should be included in the master table of data suggested as an appendix.

Response: *Information on sample size added to text.*

EI data are available from ATSDR upon request. Personal identifiers, such as location of home, are protected by confidentiality regulations.

P19/L20 Concluding paragraph on day 1 v day 2 should also evaluate also consider the continuous observations at the Oak Park site. Again, the trend plot could help.

Response: *The hourly ambient air benzene concentrations at Oak Park were added as an appendix and cited in the text.*

P20/L20 The BEI for PMA is for occupational exposure, and corresponds, more or less, to the TLV-TWA of 0.5 ppm. This is a huge level for an environmental exposure and is not a relevant comparison for lifetime environmental exposures of the general public.

Response: *ATSDR agrees that this level is not an appropriate comparison value for the general population. This is explicitly stated in the report, "The BEI was derived to protect healthy adult workers, so it may not be applicable to all segments of the general population." Nevertheless, this is the only available health-based reference value, and it is useful to include this as a point of reference.*

P21/L8 The sentence that conditions during the EI were "similar to those that occur throughout the year" is unwarranted. Atmospheric conditions influencing pollutant concentrations would include wind speed, direction, stability, mixing height, etc.; emissions obviously vary and there are not direct measures of those. Only wind direction was examined. Here, at the least, compare results to annual wind roses, as suggested above.

Response*: Text was revised and "similar" statement deleted.*

7. Are the exposure investigation results presented and interpreted appropriately and completely? Did this exposure investigation accomplish its stated objectives?
   Yes ( ) No ( ) Unsure (x)
   Why? I've pointed out a number of concerns; it is worth noting again the need to look at chronic exposure levels when looking at ongoing community exposure. The data collected are best suited to identify whether the TAMU results were anomalies, which appears quite clear; and whether some other pathway or source is affecting residents, which does not appear to be the case. However, the data analysis is incomplete, as discussed above.

   Response: *As stated in the report, "The purpose of this investigation was to measure current levels of exposure to benzene and related petroleum VOCs in residents who live near refinery row." The purpose of the EI was not to look at chronic exposure levels, nor was it intended to identify sources of ambient air contaminants.*

8. Are scientific uncertainties clearly identified and characterized?
   Yes ( ) No (x) Unsure ( )
   Why? Some uncertainties are discussed, but the analysis appears to conclude that results are sufficient to determine whether MRLs or other acute levels are or can be exceeded, and that at least one day of monitoring is "representative." The text should discuss these limitations, note that there is no way of knowing whether emissions during the sampling period where typical, and should note that the availability of the continuous data can help fill in some of these gaps.

   Response: *It is stated in the report that, "The conclusions of this health consultation are based on the time period during which the exposure investigation was conducted. The report draws no conclusion as to the potential health impact of past or future exposures." This is stated in the Conclusions, the Executive Summary, and it is discussed in the Limitations section.*

   The data from the continuous air monitoring stations will be evaluated in ATSDR's Public Health Assessment.

9. Were the limitations of the exposure investigation adequately noted?

Yes ( ) No (x) Unsure ( )
Why? See above
The EI concluded that conditions during the 2-3 day field study were similar to those that occur throughout the year based on ambient air concentrations. This has been commented elsewhere.

Response: *The text in the Limitations Section was revised.*

The EI also concludes that tobacco smoke was a major source of benzene exposures. Smoking behavior may be affected by seasons. For example, people tend to smoke indoors and close windows in both hotter and cooler seasons, leading to higher benzene exposures. For this reason, benzene concentrations attributed to smoking and ETS measured during the field study period may not represent long-term levels.

Response: *It is beyond the scope of this EI to examine the seasonal variability in tobacco smoke exposures.*

10. Are the conclusions and recommendations supported by the findings of the exposure investigation? Are the conclusions and recommendations appropriate and complete?
Yes ( ) No (x) Unsure ( )
Why? Conclusion 7 really isn't supported. This conclusion is only reasonable if the monitoring results from 2 days of sampling represent are representative. We don't know whether the sampling days were representative. Also, there are no statistics presented and the current analysis emphasizes 95th percentile values and detection frequencies,, which are not the best indicators given the sample sizes used (as discussed above)

Response: *Conclusion 7 deleted.*

The last sentence of Conclusion 8 should not be listed as a conclusion

Response: *Sentence deleted.*

P21/L27 The conclusion that VOC levels in personal air, blood, and urine samples from the EI participants were "similar" to those in NHANES is inappropriate since:

Response: *Although the reviewer is making a largely semantic point, we agree that rephrasing is useful. The word "similar" was deleted, and the conclusions were rephrased using descriptors that are statistically accurate.*

a) There were no urine samples in NHANES.

Response: *Agreed. Text revised.*

b) For the personal air samples, the geometric means of m,p-xylene, toluene, and MTBE in both non-smokers and smokers were differed between EI and NHANES.

Response: The c*onclusion was edited to be more precise with regard to statistical aspects.*

c) For blood levels in smokers, the percent of samples greater than NHANES 95th percentiles was from 8 - 12% for most VOCs, except for MTBE, and the 95th percentile concentrations of most VOCs in the EI exceeded levels in NHANES.

Response: *To explain the distribution of analytes in smokers we added this plausible hypothesis to the Discussion section: "The strong correlation of blood benzene and 2,5-DMF offers a likely explanation to why more than 5% of the EI smokers had a higher VOC levels than the reference population. The EI blood samples were collected from people in their homes where they may have recently smoked a cigarette. Thus, the blood concentrations of benzene, toluene, ethylbenzene, xylenes and 2,5-DMF from the tobacco smoke would have been near the maximum. Conversely, NHANES samples are collected at a mobile exam center where tobacco smoking is prohibited. Thus, the NHANES blood VOC data would not be influenced by tobacco smoke exposure within the last 1 – 3 hrs, whereas the EI exposure data would be."*

P22/L2 The conclusion that test results (smokers had higher VOC levels than non-smokers) for both smokers and non-smokers were "similar" to those from the comparable NHANES population is inappropriate since:

a) For personal airborne samples, geometric mean concentrations of m,p-xylene, o-xylene and toluene were not higher in smokers than non-smokers in NHANES data.

Response: *Text revised to be more statistically precise.*

b) For blood samples, the EI does not show averaged concentrations of VOCs in NHANES. It's thus impossible to compare VOC concentrations between smokers and non-smokers, or to compare the EI and NHANES more generally data.

Response: *Geometric means and confidence intervals for the EI and NHANES populations were added to the tables of blood VOC concentrations.*

P22/L9 The conclusion that risks are comparable to that of the US population is inappropriate since:

a) The age of participants in the EI and NHANES were quite different.
b) As mention, VOC levels in these datasets showed some differences, so the risks may not be comparable for all VOCs.
c) Risks were not quantified or tested statistically.

Response: *This conclusion was deleted.*

d) While the increment of additional VOC exposure from refinery sources may be small, the EI does not (and cannot) quantify risks due to mixtures, unmeasured VOCs, and other emissions. It also does not account for upset conditions.

Response: *This is beyond the scope of this EI.*

11. Are the references appropriate and relevant to the exposure investigation? If not, provide additional reference materials/information.
Yes ( ) No (x) Unsure ( )

Response: *Additional references added.*

12. Are there any other comments about the exposure investigation that you would like to make?
The investigation appears to have been competently conducted. The analysis requires a bit more analysis, but will certainly show that the earlier results were wrong. At the same time, the EI should not de-emphasize VOC contributions from the refinery sources although levels fall between acute guideline levels since the population experiences chronic exposures and since it is likely that emissions were higher in the past when fewer controls were imposed.

Response: *ATSDR's Public Health Assessment will discuss historical ambient air data and the health implications of chronic exposures.*

13. Are there any comments on ATSDR's peer review process?
Hopefully these comments are useful!

RECOMMENDATION

What is your overall recommendation on this exposure investigation? Please select the appropriate category below:

Recommend ( ).

Recommend with Required Changes (x).
List recommended changes:

Not Recommended ( ).
List reasons for not recommending:

Peer Reviewer 3: ATSDR 'Health Consultation – Exposure Investigation Biological and Environmental Monitoring for Exposure to Benzene and Related Petroleum Chemicals'

General Comments:

From a technical perspective the report is sound and the conclusions from the sampling also sound however the strength of the conclusions could be modified to reflect an investigation carried out at one point in time and hence caveats on the findings made in this context up front. The concluding comments are clear on this. One question was why there was no attempt to do a factor analysis to confirm the source (s) of exposure? This may have aided the conclusions. There are areas in the report where some clarification of approach and analysis would assist the reader in understanding the investigation. If the report is to be used for community consultation then some clarification of some of the information may be warranted to aid understanding. Please ignore the comment if this report will not be available to the public.

Response*: It was beyond the scope of the EI to conduct a factor analysis to identify the source(s) of exposure. However, we did add a multiple regression analysis to identify the independent variables that influenced the blood VOC concentrations.*

The report is a technical document aimed at an audience that is knowledgeable about environmental science. However, it will available to the public and will be posted on ATSDR's web site.

Tone of report: If this report is to be used for public consultation it is very critical of the previous TAMU work. It could offend members of the community given the collaboration that resulted in the TAMU work in the first place. I certainly felt the introduction provided critical analysis of the TAMU work which I felt would be better served later in the report. Without seeing the report its hard to comment on this aspect. As a scientific piece of work it could easily have indicated that the TAMU results were very high and needed to be confirmed. In the body of the report, the sampling and analysis issues and lack of QA/QC could be raised in the context of why the results might be different and importantly why they differ from the results of the current investigation, noting the difference in time frames of the two studies.

Response*: It is not ATSDR's intention to critique the TAMU study, but it is appropriate for us to offer possible explanations for the anomalously high test results. Other than a short summary of the results, TAMU has not publically released any details of the study. Therefore, it is not possible to compare the methodology or results of the two studies.*

Executive Summary: The Executive summary needs to make it clear that testing was undertaken a one point in time and doesn't reflect a comprehensive assessment of exposure over seasons. While comment on this is made - it is not explicit. It is unclear to an outsider whether the public health assessment will further assess exposure in this population of interest.

Response: *The Executive Summary was revised to emphasize these points. The public health assessment will comprehensively evaluate air contamination data for the site.*

Introduction: The introduction outlines the previous work by TAMU. It indicates that the methods used by the TAMU project were possibly suspect due to contamination issues. It is highly unusual for no QA/QC data to be provided and hence would be very frustrating and very poor practice. However without evidence it may be preferable to outline the high results needed investigation in the context of tried and true validated methods. As an outsider maybe I am seeing this differently to the community and others. I certainly know with my government hat on that I would not have been making such comments without very good evidence. While the methods used by the TAMU study may not have been validated – this does not necessarily mean they were wrong.

Response*: TAMU reported that the median concentration of benzene in blood samples from residents with detectable concentrations (method detection limit < 0.54 ng/ml) was 48.2 ng/ml, and the maximum concentration detected was 542 ng/ml. (Citizens for Environmental Justice, Texas A & M Health Science Center School of Rural Public Health, and Coastal Bend Health Education Center. Final Report on Results of the Hillcrest Study. January 2010.)*

These blood benzene concentrations are suspect because they far exceed blood benzene concentrations reported in occupational studies for workers in the petroleum industry, coke oven workers, gas station attendants, mechanics, and other occupations with high level exposures to benzene and petroleum products.

Methods; It would be useful for someone not familiar with this work for the overall study design to be articulated under methods so it's clear how the investigation was done and the timeframe over which testing was undertaken. This would address the target population, numbers of participants, the sampling regime etc. These details are to be found through the methods section and in results.

Field activities: It is stated that people were visited at home to reduce the influence of motor vehicle emissions from either travel or presumably filling up cars with petrol. What isn't clear is whether this was restricted for the sampling period? If not, these factors were presumably picked up by questionnaire but are not outlined in the analysis of the data. In homes residents are exposed to other sources such as wood smoke and emissions via attached garages, arts and crafts etc. Indeed in many studies cigarette smoke has had less influence on VOCs than some of these other factors. It is not clear from the report how these factors were considered?

Were residents advised not to go about their normal activities during the 48 hour sampling period? The comments therefore about contributors to exposure can't be made and it is unclear why a time activity diary wasn't used to consider other significant contributors and indeed to reflect usual exposure. If residents did not go about their normal day and the refinery emissions and other sources contributed to overall exposure, then this study may have underestimated exposure. Some clarification of this would be

good. Just as a note, it is usual for time activity diaries to be used in combination with the sampling regime so there is limited recall bias and the factors that influence VOC concentrations can be identified – particularly where industrial emissions are the subject of concern. If they were used – it is not clear nor are the results presented. This information would also be useful in outlining average exposure scenarios for this population.

Response*: The participants were given no instructions to alter their normal activities. ATSDR considered giving the participants an hourly time-activity log to record their activities, but we decided that compliance would be inadequate. Instead, we administered a questionnaire that asked people about their relevant activities during the time period of the EI. ATSDR added the results of a multiple regression analysis to the report. This analysis examines independent variables (including information from the questionnaires) that might have affected the blood VOC concentrations.*

While analysis details are provided based on methods – it is not until the results section where the QA/QC details are outlined and indeed the relevant detection limits are found. These are excellent!! The appendix is useful and perhaps should be referred to earlier in the report. Could any loss of sample result from the sample collection and shipping? In our work we actually had increased VOC concentrations despite tight shipping arrangements due to air travel and had to deal with that accordingly.

Response: We agree with the reviewer that VOCs can evaporate easily and thus special procedures are required. Since 1991, the VOC Biomonitoring Lab at CDC has been quantifying VOCs in human blood (1). Our two decades of experience in this area has led us to refine methods to minimize both handling loss and contamination gain (1-6). These carefully validated methods were the ones used for the collection, shipping, storage and analysis of VOCs in blood samples from the EI. Specifically, we collect blood samples directly from venous circuluation into a hermetically-sealed blood collection tube (1-2). This procedure minimizes evaporative loss into air during collection and storage. The materials of the blood collection tube (glass and butyl rubber) are selected to minimize VOCs partitioning out of blood and into the materials. VOC loss during sampling is minimized by removing blood for analysis by piercing the butyl rubber stopper of the collection tube to extract blood, instead of removing the stopper from the vial. This blood is immediately transferred to headspace vial and sealed for analysis. Thus, significant levels of VOCs are not lost during sample collection, storage and analysis (2).

The reviewer also mentions contamination gain. We avoid contamination by following carefully validated methods to hermetically seal collected samples and handle the samples only with materials that are relatively VOC-free. Most notably, we only collect the samples into specially-prepared glass collection tubes and stoppers (5-6). Contamination is also avoided by using VOC-free labware and solvents during the analysis.

1. *Ashley DL, Bonin MA, Cardinali FL, McCraw JM, Holler JS, Needham LL, Patterson DG Jr. (1992). Determining volatile organic compounds in human blood from a large sample population by using purge and trap gas chromatography/mass spectrometry. Analytical Chem. 1992 May 1;64(9):1021-9.*
2. *Blount BC, Kobelski RJ, McElprang DO, Ashley DL, Morrow JC, Chambers DM, and Cardinali FL (2006) Quantification of 31 Volatile Organic Compounds in Whole Blood Using Solid-Phase Microextraction and Gas Chromatography/Mass Spectrometry. J. Chromatography B 832(2):292-301; doi:10.1016/j.jchromb.2006.01.019.*
3. *Blount BC, McElprang DO, Chambers DM, Waterhouse MG, Squibb KS, LaKind JS. Methodology for collecting, storing, and analyzing human milk for volatile organic compounds. J. Environ. Monit., 2010, 12, 1265–1273. DOI: 10.1039/b927022a*
4. *Chambers DM, McElprang DO, Waterhouse MG, and Blount BC (2006). An Improved Approach for Accurate Quantitation of Benzene, Toluene, Ethylbenzene, Xylene, and Styrene in Blood. Analytical Chem. 78 (15): 5375 – 5383.*
5. *Cardinali FL, McCraw JM, Ashley DL, Bonin M, Wooten J. (1995). Treatment of vacutainers for use in the analysis of volatile organic compounds in human blood at the low parts-per-trillion level. J Chromatogr Sci. 1995 Oct;33(10):557-60.*
6. *Chambers, David M; Blount, Benjamin C; McElprang, David O; Waterhouse, Michael G; Morrow, John. Picogram measurement of volatile n-alkanes (n-hexane through n-dodecane) in blood using solid-phase microextraction to assess nonoccupational petroleum-based fuel exposure. Anal Chem 80(12): 4666-74 2008 Jun 15 (Epub 2008 May 16).*

Results:

The result are generally clear, however a number of questions arose during review that may be useful for the authors to clarify depending on the intended audience of the report.

1. What percentage of time did participants wear samplers? In studies we have done this is rarely the desired time.

Response: *The participants were instructed to wear the personal air monitors at all times. At night, they were instructed to place it on a nightstand or other location close to their bed.*

2. Given the low detection limits was the possibility of 24 hour samples not considered? This would have been good to have a look at daily variation, reduce recall bias on activities and better explain factors influencing exposure.

Response*: ATSDR collected 48-hour air samples so that the air samplers would be capable of detecting the concentrations of benzene and other VOCs that are typically*

found in ambient air. If we had collected 24-hour samples, more of the air VOC concentrations would have been below the Limit of Detection.

3. The ambient average concentrations for a year are provided in terms of ambient air, but VOC concentrations can be highly variable as shown by the range of concentrations presented for 2009 data. This can influence personal exposure concentrations and hence seasonal variation would appear to be important. Comment on this later in terms of the results may be useful.

Response: *ATSDR acknowledges that the test results are specific for the time period of the EI. Meteorological and seasonal variability, as well as activities at the refineries could affect test results. This is noted in the Executive Summary, the Limitations Section, and in the Conclusions.*

4. There is a surprisingly high number of non detect in this data set – particularly given the low detection limits? I don't have any comment to make on this but it is an interesting finding. In the NHANES studies were the non- detect percentages similar?

Response: *Relevant data are presented in Table 4. Although the same analytical methods were used for both the EI population and the NHANES population, the detection frequency for the EI population was less for most of the VOCs.*

5. No questionnaire data is provided and this may also assist the reader in the activities that may contribute to an individual's exposure – particularly pertinent in terms of community consultation. The focus in the report is on the elevated exposures, I am talking about factors across the population.

Response: *Questionnaire information was collected primarily for use in interpreting any unusually high test results that were detected. The questionnaire data were not intended to be used to investigate the variability in exposures within the normal NHANES background range of exposures.*

6. Given the blood BTEX concentrations reflect very short term exposure and may be related to activities such as filling a car with petrol, smoking etc, it is difficult to be firm about the conclusion that the mean is statistically significant one day versus the next. Indeed the difference in blood concentrations may not be reflecting outdoor emissions sources at all. Some comment to this effect might be useful. As is noted earlier depending on when exposure occurred blood concentration will be affected at the time of collection. This facet makes one wonder if blood BTEX is an appropriate marker of exposure for periods longer than 12 hours.

Response: *ATSDR conducted a multiple regression analysis to determine which factors affected blood VOC concentrations. Pumping gasoline into a car within the previous 24-hours did not have a significant effect on blood VOC concentrations. ATSDR acknowledges that blood VOC concentrations can vary from day-to-day depending on meteorological conditions, refinery activities, as well as personal activities. The report states that the test results may not be representative of the community-at-large or of other time periods.*

Limitations of EI

This section was appropriate. The only comment is that the authors comment that the ambient air concentrations were similar to those during the rest of the year. In terms of averages – yes but there may be days when concentrations are elevated. This is demonstrated by the maximum concentrations presented. Indeed the 90^{th} percentile concentrations are also elevated for the Oak Park monitoring data compared with the 22 locations the rest of the States. The conclusion may well be sound but the information is not provided in the report to support that conclusion.

Response: *The text in the limitations section was revised to indicate that the findings apply only to the time period of the EI.*