

To: Cagen, Stuart Z SHLOIL-SHOIL-SHS <stuart.cagen@shell.com>
From: Ross Macdonald <rossmacdonald@houston.rr.com>
Cc:
Bcc:
Received Date: 2006-01-19 03:44:24 GMT
Subject: Re: Proposed Benzene VCCEP Schedule for 2006

Thanks. I'll get back to you.

----- Original Message -----

From: Cagen, Stuart Z SHLOIL-SHOIL-SHS
To: Ross Macdonald
Sent: Wednesday, January 18, 2006 7:19 AM
Subject: RE: Proposed Benzene VCCEP Schedule for 2006

Strange.

Please find below some of my comments using cut and paste. I am particularly interested in your comments regarding my perception of value of the last section of the document, as shown below.

In addition (change subject to BD risk assessment), could we find some time next week to discuss the BD risk assessment. As I mentioned, I could use some help in understanding some fundamentals.

Thanks

6.1.6 Non-Cancer

6.1.6.1 Critical Study for EPA's Benzene RfC and RfD (Rothman et al., 1996)

The EPA oral reference dose (RfD) for benzene is 4.0×10^{-3} mg/kg/day and is based on a dose-related decrease in the absolute lymphocyte count (ALC) observed in benzene-exposed workers (Rothman et al., 1996). The EPA inhalation reference concentration (RfC) for benzene is 3×10^{-2} mg/m³ and is based on data from the same study. Rothman and co-workers conducted a cross-sectional study of 44 workers exposed to benzene in the workplace (inhalation), as well as 44 age- and gender-matched controls. All exposed workers and controls were from Shanghai, China. The exposed workers were selected from three types of industries with excessive benzene exposures: 1) a rubber padding manufacturing facility, 2) an adhesive tape manufacturing facility, and 3) a factory that used benzene-based paints. Exclusion criteria for potential subjects in this study included known prior exposure to ionizing radiation or chemotherapy, a prior history of cancer, or current pregnancy. The mean exposure duration for the exposed group was 6.3 years (range = 0.7-16 years). The median 8-hour time-weighted average (TWA) benzene exposure for all exposed workers was 31 ppm (99 mg/m³). The exposed population was subdivided into low (31 ppm) exposure groups. The median 8-hour TWA benzene exposures for the low and high exposure groups were 13.6 ppm and 91.9 ppm, respectively. A variety of routine hematology parameters were analyzed: total white blood count (WBC), ALC, hematocrit, red blood cell count, platelet count, and mean corpuscular volume (MCV). All six parameters were significantly different in the high exposure group (>31 ppm; median = 91.9 ppm). MCV was significantly increased; the other five parameters were significantly decreased. Several members of the low exposure group experienced exposures greater than 31 ppm on at least one day of monitoring; therefore, a subset of workers was created that did not have exposure greater than 31 ppm on any monitoring day (N = 11). These workers, selected from the low exposure group, had a median 8-hour TWA benzene exposure of 7.6 ppm (range 1-20 ppm). The only hematology parameter reported to be significantly decreased compared to controls in this subset was the ALC. As a result, lymphocytopenia (as measured by the ALC) was determined to be the most sensitive endpoint.

Benzene exposure was monitored by personal passive dosimetry badges worn by each worker for a full work shift on 5 days within a 1- to 2-week period prior to collection of blood samples. Benzene exposure was also

evaluated qualitatively through urine analysis of benzene metabolites collected at the end of the benzene exposure period for the exposed subjects. Historical benzene exposure of the subjects was also estimated via employment records.

Benchmark dose (BMD) modeling of the ALC exposure-response data from Rothman et al (1996) was done using EPA Benchmark Dose modeling software (version 1.2). The data were supralinear; therefore, in order to fit the data with a continuous linear model, the exposure levels were first transformed according to the equation $d' = \ln(d + 1)$. The parameters were estimated using the method of maximum likelihood. A default benchmark response of one standard deviation change from the control mean was selected, as suggested in draft EPA guidance (Benchmark Dose Technical Guidance Document, 2000). This default benchmark response for continuous endpoints corresponds to an excess risk of approximately 10% for the proportion of individuals below the 2nd percentile (or above the 98th percentile) of the control distribution for normally distributed effects. A 95% lower confidence limit (BMCL) on the resulting benchmark concentration (BMC) was calculated using the likelihood profile method. Transforming the results back to the original exposure scale yields a BMC of 13.7 ppm (8-hour TWA) and a BMCL of 7.2 ppm (8-hour TWA). The BMCL was chosen as a departure point for the RfC derivation. An adjusted BMCL is calculated by converting ppm to mg/m³ and adjusting the 8-hour TWA occupational exposure to an equivalent continuous environmental exposure. The adjusted BMCL (BMCLadj) was calculated to equal 8.2 mg/m³. The RfC is then derived by dividing BMCLadj by the overall uncertainty factor (UF) of 300 to yield the RfC of 3×10^{-2} mg/m³. The overall UF comprises a UF of 3 for the effect-level extrapolation, 10 for intraspecies differences (human variability), 3 for subchronic-to-chronic extrapolation, and 3 for database deficiencies.

[Not sure where to put this (or if it should be included), perhaps here perhaps in data needs (to be included): What might be included is the discussion in IRIS about alternative RfC calculations based on the Ward study : <http://www.epa.gov/iris/subst/0276.htm>; For further comparison, an RfC was also calculated, based on the NOAEL of 30 ppm from the Ward et al. (1985) study. Converting the units and adjusting for continuous exposure as above results in a NOAELADJ of 17.1 mg/m³. The NOAELADJ is then divided by an overall UF of 300 to obtain the RfC: $17.1 \text{ mg/m}^3 \div 300 = 6 \times 10^{-2} \text{ mg/m}^3$. The combined UF of 300 represents a UF of 3 for interspecies extrapolation (inhalation), 10 for intraspecies differences, 3 for subchronic-to-chronic extrapolation, and 3 for database deficiencies. The value of $6 \times 10^{-2} \text{ mg/m}^3$ is also in good agreement with the RfC of $3 \times 10^{-2} \text{ mg/m}^3$ calculated from the BMC from the Rothman et al. (1996) human study.

In order to calculate the oral RfD, an equivalent oral dose is estimated by taking the BMCLadj multiplied by the default inhalation rate. This is multiplied by 0.5 to correct for the higher oral absorption compared to inhalation, and divided by the standard default human body weight of 70 kg (equivalent oral dose = 1.2 mg/kg/day). The RfD was then derived by dividing the equivalent oral dose by the overall uncertainty factor of 300 ($4 \times 10^{-4} \text{ mg/kg/day}$). The UFs are the same as described for the RfC above.

EPA considers the BMC to be an adverse-effect level; therefore, the effect-level extrapolation analogous to the LOAEL-to-NOAEL UF was used. A factor of 3 (vs. 10) was selected, because the BMD corresponded to an adverse effect that was not very serious. Second, a factor of 10 was used for intraspecies differences in response (human variability) as a means of protecting potentially sensitive human populations. Third, a subchronic-to-chronic extrapolation factor was applied, because the mean exposure duration for the subjects in the principal study was 6.3 years (7 years is the exposure duration used by EPA for deriving chronic RfDs). However, a value of 3 (vs. 10) was selected, because it was very close to the 7-year cutoff. Finally, a UF of 3 was chosen to account for database deficiencies, because no two-generation reproductive and developmental toxicity studies for benzene are available.

also

1.1 Analysis of Risk Assessment Results (I am not sure these two arguments are necessary or sustainable as per this assessment. EPA risks are based on 70 years of exposure whereas incidences are reported as annual. Perhaps this should be discussed for clarity)

Risk assessment is an important tool that should illuminate choices, costs and priorities so public health officials can make informed decisions to protect public health. However, risk assessment is an inexact science. Many layers of conservatism are built into both the exposure assessment component and in the dose-response component where the “acceptable” exposure guideline is developed. Therefore, it is often helpful to conduct reality checks, on both the exposure assessment and the risk assessment findings to see if they make sense. The exposure assessment in this VCCEP report contains a reality check where published blood benzene biomonitoring levels were compared with predicted blood benzene concentrations (using a PBPK model and the estimated exposures from the exposure assessment). The following are some reality checks which are provided to illuminate the reasonableness of the findings from this risk assessment.

1.1.1 Incidence of Childhood Leukemia Is Increasing, Yet Levels of Benzene Are Decreasing

As summarized in Section 5.4, levels of benzene in the environment have declined substantially since the early 1970s and dramatically over the past 15 years. If benzene were to be causing increased incidences of leukemia (and specifically AML) among children, then we would expect to see some decline in the incidence of childhood leukemia in the U.S. that paralleled this decline in environmental benzene. However, the opposite is true; there has been a substantial increase in the incidence of childhood leukemia in the U.S. Most of this increase is attributed to a rise in the incidence of ALL among children. The incidence of AML, which is the most applicable to benzene exposures, among children has remained largely unchanged over the past 30 years (Ries et al., 1999).

This raises some important questions about the current theories for the causes of childhood leukemia. However, the opposing trends between historical benzene exposures and the changes in childhood leukemia incidence suggests that environmental benzene exposures are not a significant contributor towards the background incidence of childhood leukemia in the U.S.

1.1.2 Incidence of Leukemia and AML In Alaska Are No Different Than in the Continental U.S.

The available exposure information on Alaskan homes indicates that they have the potential for significantly higher indoor benzene levels than in homes in the Continental U.S. (section 7.2.1.5). The EPA default (linear) approach would predict that there should be an excess incidence of AML in Alaska compared to the rest of the U.S. This possibility was investigated by analyzing the Alaska cancer registry (Alaska, 2000a; 2000b). The reports for 1997 (Alaska, 2000a) and 1998 (Alaska 2000b) contain incidence and mortality data on specific leukemia subtypes. The Alaska reports provide age-adjusted rates of incidence and mortality (per 100,000 individuals) and confidence intervals for each and the incidence and mortality rate for the continental U.S. for each leukemia subtype. In the 1997 report, the cancer incidence for leukemias were broken into subtypes of origin of cell-line (myeloid, lymphocytic, monocytic, other) but did not differentiate between acute or chronic. The incidence of myeloid leukemias in 1997 in Alaska was 3.9 per 100,000 (95% CI: 2.2 - 6.6) and the US rate for the years 1993-1997 was reported as 4.4 per 100,000 (Alaska 2000a), suggesting no significant difference between the two. The report for the 1998 cancer registry provided more refined disease classification which allowed for a comparison of specifically AML, the disease of concern with benzene. The incidence of AML in 1998 in Alaska was 3.3 per 100,000 (95% CI: 1.7 – 5.9) and 2.8 in the U.S. for the years 1994 – 1998, again demonstrating no difference between the incidence of AML in Alaska and the U.S. There appears to be no difference in the incidence of leukemia (the subtypes of leukemia were not broken out in the Alaska report) between whites and Alaska natives (Alaska 2000b). AML incidence data for Alaska is not consistent with the hypothesis that Alaskan children are at higher risk due to increased benzene exposure.

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-----Original Message-----

From: Ross Macdonald [<mailto:rossmacdonald@houston.rr.com>]
Sent: Tuesday, January 17, 2006 9:01 PM
To: Cagen, Stuart Z SHLOIL-SHOIL-SHS
Subject: Re: Proposed Benzene VCCEP Schedule for 2006

Still no.

----- Original Message -----

From: "Cagen, Stuart Z SHLOIL-SHOIL-SHS"
To: "Ross Macdonald"
Sent: Tuesday, January 17, 2006 6:58 PM
Subject: RE: Proposed Benzene VCCEP Schedule for 2006

Stuart Cagen

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-----Original Message-----

From: Ross Macdonald [<mailto:rossmacdonald@houston.rr.com>]
Sent: Tuesday, January 17, 2006 6:47 PM
To: Cagen, Stuart Z SHLOIL-SHOIL-SHS
Subject: Re: Proposed Benzene VCCEP Schedule for 2006

Stuart: My filter quarantines your attachment as a .zm9. I don't think you are a spammer but could you resend it?

The same thing has happened to some of Ralph's e-mails so you might ask him what the deal is.

Ross

----- Original Message -----

From: "Cagen, Stuart Z SHLOIL-SHOIL-SHS"

To:

Cc: ; ;

"Clegg, Patsy M SCC-DCS/22"

Sent: Tuesday, January 17, 2006 5:19 PM

Subject: RE: Proposed Benzene VCCEP Schedule for 2006

I cannot recall who I was supposed to send my comments to. I have added some comments to Patsy's version.

Let me know if you questions, etc

Thanks

Stuart Cagen

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