A Cohort-Based Approach for Characterizing Lifetime Inhalation Cancer Risk from Time-Varying Exposure to Air Toxics

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ABSTRACT

In recent years, the U.S. EPA as well as State and local agencies have released a number of risk characterizations addressing potential inhalation cancer risks from exposure to ambient sources of air toxics (e.g., U.S. EPA’s 1993 Motor Vehicle-Related Air Toxics Study, the South Coast Air Quality Management District’s MATES-II study, the U. S. EPA’s National Scale Air Toxics Assessment). In these assessments, quantitative estimates of cancer risk are often presented as point estimates and/or distributions of individual upper-bound lifetime risks. The individual upper-bound lifetime cancer risk is the probability that an individual in a given population will contract cancer if exposed continuously to a given concentration of an airborne carcinogen over an assumed lifetime. Individual risk estimates in these studies are usually based on average or median exposures for a wide population distribution.

These estimates generally assume continuous exposure over an entire lifetime to levels estimated for one or a few years, and do not account for expected changes in exposure over time. For example, risk estimates in U. S. EPA’s recent National Scale Air Toxics Assessment assume individuals will be exposed to 1996 levels over a 70-year lifetime. However, exposures to most air toxics are expected to change over time as a result of mobile and stationary source emission control programs.
In this paper, a cohort-based approach, which estimates individual lifetime cancer risk based on time-weighted exposure over a lifetime, is presented. This approach accounts for changes in exposure level over time, including decreases anticipated as a result of regulatory programs. It also incorporates differences in exposures to children and adults that result from certain differences in time-activity patterns, integrating them into a single value for a cohort. Moreover, this paper presents a case study applying this approach to estimate average nationwide individual cancer risks from exposure to the highway mobile source contribution to ambient benzene. The case study includes estimates for the general population and a highly exposed demographic group, outdoor workers.

INTRODUCTION

In recent years, the U.S. EPA as well as State and local agencies have released a number of risk characterizations addressing potential inhalation cancer risks from exposure to ambient sources of air toxics. Some studies estimate cancer risk assuming that individual exposures are equivalent to average ambient concentrations in a given area;\textsuperscript{1} whereas other studies attempt to estimate risk based on modeled exposures.\textsuperscript{2, 3} Modeled exposures are calculated by predicting microenvironmental air concentrations based on ambient concentrations and combining these microenvironmental air concentrations with data on human activity patterns. In these assessments, quantitative estimates of cancer risk are often presented as point estimates and/or distributions of individual upper-bound lifetime risks. The individual upper-bound lifetime cancer risk is the probability that an individual in a given population will contract cancer if exposed continuously to a given concentration of an airborne carcinogen over an assumed lifetime. Individual risk estimates in these studies are usually based on average or median exposures for a wide population distribution.

These estimates generally assume continuous exposure to levels estimated for one or a few years over an entire lifetime, and do not account for expected changes in exposure over time. For example, risk estimates in U.S. EPA’s recent National Scale Air Toxics Assessment assume individuals will be exposed to 1996 levels over a 70-year lifetime.\textsuperscript{3} Thus, these estimates do not take into account significant reductions in emissions that have taken effect since 1996, future reductions anticipated from mobile and stationary source control programs, facility closures, industry initiatives and so on. EPA has projected that the mobile source contribution to ambient concentrations of gaseous hazardous air pollutants will decrease by 24 and 50% between 1996 and 2007, depending on the pollutant.\textsuperscript{4, 5} Furthermore, in its recent mobile source air toxics rule, EPA projects that, between 1990 and 2020, these programs will reduce on-highway emissions of benzene, formaldehyde, 1,3-butadiene and acetaldehyde by 67 to 76 percent.\textsuperscript{6} There will be substantial reductions from nonroad mobile sources as well. Among the programs that lead to these reductions are reformulated gasoline (RFG) and anti-dumping standards, the national low emission vehicle (NLEV) program; Tier 2 motor vehicle emissions standards and gasoline sulfur control requirements; and heavy-duty engine and vehicle standards and on-highway diesel fuel sulfur control requirements.
In this paper, a cohort-based approach, which estimates individual lifetime cancer risk based on time-weighted exposure over a lifetime, is presented. This approach accounts for changes in exposure level over time, including decreases anticipated as a result of regulatory programs. It also incorporates differences in exposures to children and adults that result from certain differences in time-activity patterns. Methods have been developed in the past to estimate population risk over long periods of time where exposures vary, in particular for ground water contamination of aquifers near hazardous waste facilities.\textsuperscript{7,8}

This paper also presents a case study applying this approach to estimate average nationwide individual cancer risks from exposure to the highway mobile source contribution to ambient benzene, contrasting it to estimates which assume continuous lifetime exposure to levels estimated for a single year. The case study is based on average nationwide highway mobile source exposure estimates for base years 1990 and 1996, and projected exposures for 2007 and 2020. These exposure estimates are obtained from an EPA modeling analysis done to support several recent highway mobile source regulations.\textsuperscript{6,9,10,11,12}

**METHODOLOGY**

A methodology was developed for estimating average or median individual exposure for a population cohort born in a specific year, followed over a 70-year lifetime. This methodology requires projected annual average or median exposure estimates for various time increments in that 70-year lifetime. The more years for which exposure projections are available, the more accurate the time-weighted exposure estimates will be. In addition, the cohort approach incorporates differences in exposures estimated for children and adults. General population cohorts are based on 17 years of childhood exposure followed by 53 years of adult exposure (70 years total). The general form of the equation used to estimate time-weighted average or median exposure is as follows:

**Equation 1.** Estimation of time-weighted average or median exposure.

\[
\frac{(TI_1 \times (E_{yrA-Child} + E_{yrB-Child})) + (TI_2 \times (E_{yrB-Child} + E_{yrC-Child})) + ... + (TI_N \times (E_{yrX-Adult} + E_{yrZ-Adult}))}{70\text{yr}}
\]

\[
E = \frac{2}{2} \cdot \frac{2}{2} \cdot \frac{2}{2}
\]
Where:

\[ T_{I_n} = \text{Time interval in years} \]
\[ E_{yrA - \text{Child}} = \text{Exposure in year } A \text{ for a child} \]
\[ E_{yrZ - \text{Adult}} = \text{Exposure in year } Z \text{ for an adult} \]

Average or median individual risk for a population is then calculated by multiplying the time-weighted average or median exposure by the cancer unit risk estimate. The same approach would be used to estimate risk for individuals in any percentile of the exposure distribution for a population. This approach can also be modified to estimate risk based on time-weighted exposure for individual demographic groups (such as outdoor workers) where data are available.
BENZENE CASE STUDY

Annual Average Exposure Estimates

EPA’s recent National Scale Air Toxics Assessment (NSATA) estimated inhalation exposure to benzene, as well as 32 other hazardous air pollutants, from outdoor sources in 1996. The assessment focused on average and median exposures, rather than individual extremes. Estimates of median exposures were calculated at the census tract level, but presented at the county level and above, since results are very uncertain for individual census tracts. Table 1 presents the average of median exposures across all U. S. census tracts, as well as 5th and 95th percentile exposures and the contribution to the average from individual source sectors.

These estimates were developed using the the Hazardous Air Pollutant Exposure Model, version 4 (HAPEM4) exposure model. HAPEM4 estimates exposures based on measured or modeled ambient concentrations. In the NSATA, modeled concentrations are obtained from the Assessment System for Population Exposure Nationwide (ASPEN) model. This model is based on the EPA’s Industrial Source Complex Long Term model (ISCLT2) which simulates the behavior of the pollutants after they are emitted into the atmosphere. While ASPEN accounts for the contribution of emission sources within a 50 kilometer impact zone to census tract concentrations, the contribution of sources outside this 50 kilometer impact zone may be significant. ASPEN accounts for this, contributions from natural sources, and long-range transport through a “background” component. This component is based on monitored data and the values were obtained from the Cumulative Exposure Project. From Table 1, it can be seen that onroad mobile sources account for approximately half of exposure to ambient benzene nationwide. Onroad sources also contribute substantially to the background level as well, although it is not possible to quantify the magnitude of the contribution.

NSATA provides the best currently available average benzene inhalation exposure estimates at the national scale, despite significant limitations. However, projected estimates of exposures in future years have not been developed using the NSATA modeling approach. Thus, for the purposes of illustrating the cohort-based approach for estimating time-weighted exposure, earlier estimates of benzene exposure developed using version 3 of the HAPEM model (HAPEM-MS3) are used. Although HAPEM-MS3 estimates are available for 10 urban areas as well as nationwide annual average estimates, the nationwide annual average estimates are used in this case study. HAPEM-MS3 estimates the highway mobile source contribution to inhalation exposure, and uses carbon monoxide (CO) as a tracer for toxics exposure. Since most ambient CO comes from cars and light trucks, it is a reasonable surrogate for exposure to benzene emissions from highway mobile sources. Details of the HAPEM-MS3 modeling approach are described in the technical support document for EPA’s recent mobile source air toxics rule.

<table>
<thead>
<tr>
<th>Source Sector</th>
<th>5th Percentile</th>
<th>95th Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onroad Mobile</td>
<td>50%</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Average Nationwide Benzene Exposures from NSATA.
<table>
<thead>
<tr>
<th>Source Category</th>
<th>Percentile</th>
<th>Concentration (μg/m³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Sources</td>
<td>5th</td>
<td>0.46</td>
</tr>
<tr>
<td>All Sources</td>
<td>95th</td>
<td>2.98</td>
</tr>
<tr>
<td>All Sources</td>
<td>Average</td>
<td>1.41</td>
</tr>
<tr>
<td>Major</td>
<td>Average</td>
<td>0.02</td>
</tr>
<tr>
<td>Area and Other</td>
<td>Average</td>
<td>0.07</td>
</tr>
<tr>
<td>Onroad</td>
<td>Average</td>
<td>0.71</td>
</tr>
<tr>
<td>Nonroad</td>
<td>Average</td>
<td>0.21</td>
</tr>
<tr>
<td>Background</td>
<td>----------</td>
<td>0.41</td>
</tr>
</tbody>
</table>

There are a number of significant limitations in using the HAPEM-MS3 approach to estimate exposure to benzene from highway mobile sources. First, the model does not account for exposures to emissions originating within microenvironments. An example is exposure to benzene from vehicle evaporative emissions in attached garages, which can intrude into the residence. This source of exposure can be substantial. This limitation also applies to HAPEM4 estimates. HAPEM-MS3 also does not account for the contribution to exposure from nonroad, major, or area sources. Moreover, the model does not take into account the fact that spatial and temporal allocation of benzene evaporative emissions is different than CO emissions (However, in modern technology vehicles, benzene emissions are dominated by the exhaust component). In addition, HAPEM-MS3 uses typical activity patterns for individual demographic groups from 3 areas, and does not account for individual variation in activity within demographic groups. Finally, the data used to develop factors relating ambient levels to microenvironmental levels are very limited, obtained from only two cities.

Table 2 presents HAPEM-MS3 nationwide annual average benzene exposures attributable to highway mobile sources for 3 demographic groups – the overall population, outdoor workers, and children – in 1990, 1996, 2007, and 2020. These estimates include implementation (at the appropriate time) of Phase II reformulated gasoline, the National Low Emission Vehicles Program, Tier 2 emission standards with low sulfur gasoline, and 2004 heavy duty vehicle standards. They do not include recently finalized 2007 heavy duty vehicle standards, which would affect the 2020 estimates. These exposure estimates also do not reflect revised base year benzene emission estimates for heavy duty vehicles developed for this rule. However, these

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⁶HAPEM4 relies on a newer, more extensive activity database (the Consolidated Human Activity Database) and uses methods that account for more of the population variation in activity patterns.
revisions have very little impact on overall exposure estimates.\textsuperscript{6} Variation in estimated exposures among demographic groups is the result of differences in typical activity patterns. Differences in effective dose (differences in absorption due to physiological factors) between adults and children are not accounted for. Exposures for children are slightly lower than for the general population because children spend a little more time indoors than most other demographic groups.

**Table 2.** HAPEM-MS3 Nationwide Annual Average Highway Mobile Source Benzene Exposures for Three Demographic Groups.

<table>
<thead>
<tr>
<th>Calendar Year</th>
<th>Overall Population Exposure (μg/m(^3))</th>
<th>Outdoor Worker Exposure (μg/m(^3))</th>
<th>Children’s Exposure (μg/m(^3))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>1.067</td>
<td>1.24</td>
<td>1.02</td>
</tr>
<tr>
<td>1996</td>
<td>0.68</td>
<td>0.79</td>
<td>0.65</td>
</tr>
<tr>
<td>2007</td>
<td>0.36</td>
<td>0.41</td>
<td>0.34</td>
</tr>
<tr>
<td>2020</td>
<td>0.28</td>
<td>0.21</td>
<td>0.26</td>
</tr>
</tbody>
</table>

The HAPEM-MS3 estimate of the highway mobile source contribution to nationwide ambient benzene exposure in the general population for 1996 is very close to the HAPEM4 based estimate in Table 1. Although the emission inventories used to do the exposure modeling are almost the same, developed using the MOBTOX5b emissions model,\textsuperscript{10} the methods used are very different. Thus, the closeness of the estimates is surprising. However, estimates for individual areas can vary substantially. For instance, while the HAPEM-MS3 based estimate for average motor vehicle-related benzene inhalation exposure in Cook County, Illinois is about 0.7 μg/m\(^3\) in 1996, the HAPEM4 based estimate for average motor vehicle-related benzene inhalation exposure in Cook County is about 1.3 μg/m\(^3\).

**Calculation of Time-Weighted Exposures**

Appendix A provides the formulas used to calculate the time-weighted average exposures for cohorts beginning in the four calendar years where exposure levels changed (1990, 1996, 2007, and 2020). Separate formulas were used for general population cohorts and outdoor worker cohorts. As mentioned previously, the cohort approach incorporates differences in exposures as a result of activity patterns between children and adults. General population cohorts are based on 17 years of childhood exposure followed 53 years of adult exposure (70 years total). Outdoor worker cohorts are based on 17 years of childhood exposure, followed by 40 years of outdoor worker exposure, and 13 years of (general population) adult exposure. Figure 1 illustrates this approach for the general population.

**Figure 1.** Calculation of 1990 General Population Cohort Average Motor Vehicle Benzene
Inhalation Exposure.

The 1990 cohort lifetime average exposure concentration is calculated using the average of 1990 and 1996 exposure concentrations (children) for 1990 to 1995, the average of 1996 and 2007 exposure concentrations (children) for 1996 to 2006, the average of 2007 and 2020 exposure concentrations (general population) for 2007 to 2019, and 2020 exposure concentrations (general population) for 2020 to 2059 (i.e., a total of 70 years exposure). This approach assumes constant 2020 exposure levels after 2020, in the absence of modeling beyond that year. The other cohorts (1996, 2007, and 2020) were treated analogously. Table 3 presents time-weighted exposure estimates for general population and outdoor worker cohorts.

**Estimation of Highway Mobile Source Contribution to Benzene Inhalation Lifetime Cancer Risk**

EPA has classified benzene as a known human carcinogen based on convincing data from occupational epidemiological studies and supporting data from animal studies. EPA has stated that the data indicate a clear causal relationship between benzene exposure and acute nonlymphocytic leukemia and suggest a relationship between benzene exposure and chronic nonlymphocytic leukemia and chronic lymphocytic leukemia. Furthermore, exposure to benzene cannot be ruled out as a potential contributor to development of leukemia in children. Several occupational studies are available for derivation of the unit risk estimates. A study of
Pliofilm rubber workers is the basis for EPA’s estimates. A linear extrapolation model was used to estimate risks in the low-dose region. A range of cancer unit risk values was derived using this model based on different exposure estimates for the study population. Accordingly, the maximum likelihood (MLE) inhalation unit risk values provided by EPA range from $2.2 \times 10^{-6}$ to $7.8 \times 10^{-6}$ (μg/m$^3$)$^{-1}$. In this illustrative case study, the upper end of this MLE range is used. Average nationwide individual cancer risks attributable to benzene from highway mobile sources are calculated as the product of the time-weighted cohort average exposures and unit risk value. These estimates are presented in Table 3.

**Table 3.** Time-Weighted Average Benzene Inhalation Exposures and Individual Risk Estimates Attributable to Motor Vehicles for Population Cohorts

<table>
<thead>
<tr>
<th>Cohort Year</th>
<th>Outdoor Worker Average Exposure (μg/m^3)</th>
<th>General Population Average Exposure (μg/m^3)</th>
<th>Outdoor Worker Individual Average Cancer Risk (based on upper end of MLE range)</th>
<th>General Population Individual Average Cancer Risk (based on upper end of MLE range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>0.39</td>
<td>0.37</td>
<td>$3.1 \times 10^{-6}$</td>
<td>$2.8 \times 10^{-6}$</td>
</tr>
<tr>
<td>1996</td>
<td>0.34</td>
<td>0.32</td>
<td>$2.7 \times 10^{-6}$</td>
<td>$2.5 \times 10^{-6}$</td>
</tr>
<tr>
<td>2007</td>
<td>0.30</td>
<td>0.28</td>
<td>$2.4 \times 10^{-6}$</td>
<td>$2.2 \times 10^{-6}$</td>
</tr>
<tr>
<td>2020</td>
<td>0.30</td>
<td>0.27</td>
<td>$2.3 \times 10^{-6}$</td>
<td>$2.1 \times 10^{-6}$</td>
</tr>
</tbody>
</table>

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*It should be noted that EPA’s benzene unit risk values are actually based on a 76-year (rather than standard 70-year) lifetime.*
The risk estimate attributable to motor vehicle exposure, assuming continuous lifetime exposure to 1996 levels, would be $5.3 \times 10^{-6}$, based on HAPEM-MS3 modeling results for the general population. A similar estimate would be obtained using results from the NSATA. It should be noted that the average benzene nationwide inhalation cancer risk from all outdoor sources would be substantially higher. The estimate from the NSATA is about $1.1 \times 10^{-5}$, and the 95th percentile risk is about twice as high. In some hot spots risks are likely to be much higher. Furthermore, inhalation risk from outdoor sources represents a fraction of the total benzene inhalation risk. For instance, data from the National Human Exposure Assessment Survey (NHEXAS), which was conducted in the six States comprising EPA’s Region 5, indicate an average personal inhalation exposure to benzene of about $7.6 \mu g/m^3$. The NHEXAS data were collected from 1995 to 1997. This average measured personal benzene exposure is more than five times higher than the average inhalation exposure estimate for 1996 from outdoor sources in the NSATA.

CONCLUSION

In assessing cancer risks from exposure to air toxic emissions, risk estimates generally assume continuous exposure to levels estimated for one or a few years over an entire lifetime. Such estimates can be misleading, as they do not take into account significant reductions in emissions resulting from control programs. They are also not very useful for comparing control programs where the timing of exposure reductions varies. This paper presents a methodology that accounts for changes in exposure over time, by estimating risk for a cohort born in a specific year, using time-weighted average exposure. The case study used to illustrate this approach relies on data for benzene with significant limitations. For instance, exposure estimates are only available for four calendar years, and only exposure to highway mobile source benzene is accounted for. Nonetheless, in the absence of projected exposure estimates developed using improved methods and tools, this case study provides an informative illustration of the approach. Future assessments should account for projected changes in exposure where feasible.

REFERENCES

1. South Coast Air Quality Management District. 1999. Multiple Air Toxics Exposure Study in the South Coast Air Basin – MATES-II


**KEY WORDS**

cancer risk

risk characterization

time-varying exposure

highway mobile sources

benzene
APPENDIX – FORMULAS USED TO CALCULATE TIME-WEIGHTED COHORT EXPOSURES

General Population Cohort Formulas

1990 Cohort -- General Population

\[
E = \left\{ \frac{6\text{yr} \times (E_{1990, C} + E_{1996, C}) + (11\text{yr} \times (E_{1996, C} + E_{2007, C})) + (13\text{yr} \times (E_{2007, G} + E_{2020, G})) + (40 \times E_{2020, G})}{70\text{yr}} \right\}^{2/2}
\]

1996 Cohort -- General Population

\[
E = \left\{ \frac{11\text{yr} \times (E_{1996, C} + E_{2007, C}) + 6\text{yr} \times [(E_{2020, C} - E_{2007, C}) \times 3] + E_{2007, C}}{7\text{yr} \times [(E_{2020, G} - E_{2007, G}) \times 9.5] + E_{2007, G}} + (46 \times (E_{2020, G}))}{70\text{yr}} \right\}^{2/13}
\]

2007 Cohort -- General Population

\[
E = \left\{ \frac{13\text{yr} \times (E_{2007, C} + E_{2020, C}) + (4\text{yr} \times E_{2020, C}) + (53\text{yr} \times E_{2020, G})}{70\text{yr}} \right\}^{2/2}
\]
2020 Cohort -- General Population

\[
E = \{(17\text{yr} \times E_{2020,C}) + (53\text{yr} \times E_{2020,G}) + 70\text{yr}\}
\]

Key

\begin{tabular}{ll}
E & Exposition \\
C & Child \\
G & General population (adult) \\
O & Outdoor worker
\end{tabular}
Outdoor Worker Cohort Formulas

1990 Cohort Formula – Outdoor Workers

\[
E = \frac{(6\text{yr} \times (E_{1990-C} + E_{1996-C})) + (11\text{yr} \times (E_{1996-C} + E_{2007-C})) + (13\text{yr} \times (E_{2007-C} + E_{2020-O})) + (27\text{yr} \times E_{2020-O}) + (13\text{yr} \times E_{2020-G})}{70\text{yr}}
\]

1996 Cohort Formula – Outdoor Workers

\[
E = \frac{(11\text{yr} \times (E_{1996-C} + E_{2007-C})) + 6\text{yr} \times [(E_{2020-C} - E_{2007-C}) \times 3] + E_{2007-C} + 7\text{yr} \times [(E_{2020-O} - E_{2007-O}) \times 9.5] + E_{2007-O}}{70\text{yr}}
\]

2007 Cohort Formula – Outdoor Workers

\[
E = \frac{(13\text{yr} \times (E_{2007-C} + E_{2020-C})) + (4\text{yr} \times E_{2020-C}) + (40\text{yr} \times E_{2020-O}) + (13\text{yr} \times E_{2020-G})}{70\text{yr}}
\]

2020 Cohort Formula – Outdoor Workers

\[
E = \frac{(17\text{yr} \times E_{2020-C}) + (40\text{yr} \times E_{2020-O}) + (13\text{yr} \times E_{2020-G})}{70\text{yr}}
\]