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A methodological frame for assessing benzene induced leukemia risk mitigation due to policy measures

Spyros P. Karakitsios [a], Dimosthenis A. Sarigiannis [a,b,*], Alberto Gotti [b], Pavlos A. Kassomenos [c], Georgios A. Pilidis [d]

[a] Aristotle University of Thessaloniki, Department of Chemical Engineering, 54124 Thessaloniki, Greece
[b] Centre for Research and Technology Hellas (CE.R.T.H.), 57001, Thessaloniki, Greece
[c] University of Ioannina, Department of Physics, Laboratory of Meteorology, GR-45110 Ioannina, Greece
[d] University of Ioannina, Department of Biological Appl. and Technologies, GR-45110 Ioannina, Greece

HIGHLIGHTS

- A comprehensive exposure analysis is greatly facilitated by the thorough use of measurement data and modeling tools.
- Incorporation of internal dose metrics contributes to significant refinement of exposure assessment.
- Similar community policies have completely different effect with respect to different countries/cities.

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ABSTRACT

The study relies on the development of a methodology for assessing the determinants that comprise the overall leukemia risk due to benzene exposure and how these are affected by outdoor and indoor air quality regulation. An integrated modeling environment was constructed comprising traffic emissions, dispersion models, human exposure models and a coupled internal dose/biology-based dose–response risk assessment model, in order to assess the benzene imposed leukemia risk, as much as the impact of traffic fleet renewal and smoking banning to these levels. Regarding traffic fleet renewal, several "what if" scenarios were tested. The detailed full-chain methodology was applied in a South-Eastern European urban setting in Greece and a limited version of the methodology in Helsinki.

Non-smoking population runs an average risk equal to $4.1 \cdot 10^{-5}$ compared to $23.4 \cdot 10^{-5}$ for smokers. The estimated lifetime risk for the examined occupational groups was higher than the one estimated for the general public by 10–20%. Active smoking constitutes a dominant parameter for benzene-attributable leukemia risk, much stronger than any related activity, occupational or not.

From the assessment of mitigation policies it was found that the associated leukemia risk in the optimum traffic fleet scenario could be reduced by up to 85% for non-smokers and up to 8% for smokers. On the contrary, smoking banning provided smaller gains for (7% for non-smokers, 1% for smokers), while for Helsinki, smoking policies were found to be more efficient than traffic fleet renewal.

The methodology proposed above provides a general framework for assessing aggregated exposure and the consequent leukemia risk from benzene (incorporating mechanistic data), capturing exposure and internal dosimetry dynamics, translating changes in exposure determinants to actual changes in population risk, providing a valuable tool for risk management evaluation and consequently to policy support.

1. Introduction

Exposure to benzene constitutes a major environmental concern, since it is considered as an established cause of acute myeloid leukemia (AML), myelodisplastic syndromes (MDS), and probably lymphocytic leukemia and non-Hodgkin lymphoma (NHL) in humans (Zhang et al., 2010). Although urban ambient air levels in most European cities are within the limits imposed by the related legislation (E.C., 2000) according to several recent campaigns (Edwards and Jantunen, 2001; Fondelli et al., 2008; Kotzias et al., 2009; Manini et al., 2006), in Greece, benzene concentrations are still elevated (Chatzis et al., 2005; Pilidis et al., 2005; Pilidis et al., 2009) mainly due to specific features of the traffic fleet composition. Indoor benzene concentrations follow a similar pattern (Jantunen et al., 1999), due to outdoor benzene penetration, as

* Corresponding author at: Environmental Engineering Laboratory, Department of Chemical Engineering, Aristotle University of Thessaloniki, University Campus, Bldg. D, Rm 201, 54124 Thessaloniki, Greece. Tel.: +30 2310 994562.
E-mail address: denis@eng.auth.gr (D.A Sarigiannis).

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well as strong indoor sources, the presence of Environmental Tobacco Smoke (ETS) being the dominant among them (Aquilina et al., 2010; Heavner et al., 1995); (Lai et al., 2007). For smokers, mainstream tobacco smoke has been found to be the dominant source of exposure (Wallace, 1989, 1990); considering that 36% of the adult population in Greece are smokers (WHO, 2008).

In Greece, a smoking ban in public indoor places was recently applied (as of 1/7/2009), while an organized plan of traffic fleet renewal is being contemplated. Considering that both policies will have an effect on the overall benzene exposure levels (among several other pollutants), quantifying each policy contribution to benzene aggregate exposure and to the related leukemia risk mitigation is of particular interest.

The specific tasks that need to be addressed for such a quantitative estimation include:

- The assessment of current levels of ambient air and personal exposure to benzene.
- The quantification of the relative contribution of exposure determinants.
- The estimated risk under the current levels of exposure.
- The relative effect of policies (possible traffic fleet renewal scenarios and smoking banning) on the overall exposure and the associated leukemia risk.

In order to respond to the needs of the study, a methodological approach was developed coupling modeling and experimental data. Although the study was based on extended measurements performed in a specific location, the overall methodology is general. It provides a wider framework for similar studies aiming to assess aggregate exposure and the determinants of multiple source air contaminants. As for evaluating the policy measures in the wider Greek region, it needs to be clarified that the experimental part of the study was conducted in an area where extended data on benzene existed through a series of studies carried out by the authors, including several environmental settings (Karakitsios et al., 2006, 2007a; Kassomenos et al., 2004, 2005; Pilidis et al., 2005) and population groups, occupational (Karakitsios et al., 2007b; Pilidis et al., 2009; Sarigiannis et al., 2009c) or not (Karakitsios et al., 2010). These studies showed that the prevailing air pollution characteristics are quite representative for the whole country, taking into account that ambient air benzene and exposure levels (Pilidis et al., 2005, 2009) are known to be at the same levels in Athens (Chatzis et al., 2005) and Thessaloniki (Kotzias et al., 2009; Vlachokostas et al., 2011), which are the largest scale urban areas (with 5 and 1 million inhabitants respectively). Leukemia risk was assessed through a Physiology Based PharmacoKinetic (PBPK) model, coupled to a Biology Based Dose Response (BBDR) model. Mechanistic approaches at carcinogenic risk assessment process started by the development of biologically motivated cancer risk models (Moolgavkar and Dewanji, 1988; Thorslund et al., 1987). Low-dose refined estimates (Cox, 1996; Crump, 1994b), are in compliance to the latest findings on leukemia etiology (Smith, 2010; Zhang et al., 2010). The added value of coupled PBPK–BBDR models in comparison to solely epidemiological exposure response functions is that they provide biology based knowledge of the mechanisms of chemical toxicity (Chiu et al., 2007; Sarigiannis et al., 2009b); this is a more rational and sophisticated way for estimating potential health implications than statistical relations extrapolated from epidemiological studies. As such, they can be valuable tools for improving the physiological and biological bases of regulatory health risk assessment.

2. Methodology

2.1. Measurements — data utilized

The measurement campaign included ambient air monitoring of benzene in 13 points in the city and personal exposure monitoring involving 20 volunteers with the method of passive sampling. From the 20 volunteers, 8 of them were smokers. Smoking was going to be a significant confounder if biomonitoring data were taken. Since the experimental part of the study was limited to environmental monitoring, this was affecting only indoor air quality, which is incorporated in the calculations in terms of ETS presence (even if the source of ETS might be the smoker himself). The samplers were exposed for one week and the campaign was performed in a similar way in the summer and winter to account for seasonal variation. The volunteers kept a detailed time activity diary (TMAD) similar to the one in the EXPOLIS study (Lai et al., 2007). Furthermore, active sampling was performed in urban street canyons, as well as for personal exposure under different activities. The active sampling time (personal or ambient) was 30′ and a very high time resolution of measurement results was obtained throughout the campaigns. In parallel to the above measurements, traffic measurements in the main streets of the city related to fleet composition were performed and meteorological conditions (wind speed-direction and ambient air temperature) were recorded. Similar sampling protocols were kept in exposure assessment of occupational groups highly exposed to benzene, either to elevated exposure to traffic pollutants (traffic policemen and taxi drivers), or due to the nature of work (gasoline station employees). Details on the experimental procedures (samplers, laboratory equipment, analytical methods and QA/QC) are already presented elsewhere (Karakitsios et al., 2007a; Pilidis et al., 2009).

2.2. Modeling tools

Urban benzene concentrations were modeled based on the obtained traffic and meteorological data by applying several well-known and validated models such as COPERT III (Ntziachristos and Samaras, 2000), CALINE 4 (Benson, 1992) and OSPM (Berkowicz, 2000), as well as in-home models (Karakitsios et al., 2006; Kassomenos et al., 2004). Modeling the concentrations of the wider urban area was crucial for dividing the city in location zones (based on the levels of ambient air benzene) and time zones (based on the traffic activity and the related diurnal variation of ambient air benzene levels). Individual exposure was modeled by stepwise linear regression of the exposure measurements using the information collected by the TMAD (Karakitsios et al., 2010).

Of particular interest is the methodological approach used to evaluate leukemia risk due to exposure to benzene. For this purpose, a PBPK model was coupled to a biology based dose–response (BBDR) model for risk assessment. Physiologically based pharmacokinetic/dynamic (PBPK/PD) models propose a realistic even if simplified description of the mechanisms of absorption, distribution, metabolism and elimination of chemicals in the body. In these models, the body is subdivided into various compartments representing specific organs or homogeneous groups of tissues linked and irrigated by blood vessels. Compartments are characterized by a set of parameters of physiological relevance (e.g., volume or blood perfusion rate) which play a crucial role in explaining the behavior of chemical substances in the body, and represent invariants across substances. Physiologically based pharmacokinetic (PBPK) models provide a parametric framework suitable for dealing with extrapolations between species, routes or dose levels.

The model for benzene and the related toxic metabolites is a six-compartment model (Fig. 1). The six tissue groups include: liver (main metabolic tissue); adipose tissue (FAT); richly perfused tissues (RTP); poorly perfused tissues (PPT); bone marrow (the main target organ for benzene toxicity) and the kidney; each one interconnected to the others by systemic circulation and a gas-exchange lung. The bone marrow was included because it is recognized as the main site manifesting benzene toxicity (i.e., leukemia) and because it is, together with the kidney, a potential site benzene metabolism. The liver was further subdivided into three equal volume sub-compartments