行政院國家科學委員會專題研究計畫　成果報告

環境暴露評估利用人體藥物動力學模式體內濃度測量值

計畫類別：個別型計畫
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執行期間：93 年 08 月 01 日至 94 年 07 月 31 日
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計畫主持人：陳主智

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（計畫名稱）

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共同主持人：
計畫參與人員：　陳主智，施銘權，陳德佑，翁仕旻

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中　華　民　國　95　年　3　月　4　日

中英文摘要

傳統環境暴露評估常會有採樣點測量值變異數過大與不易確定污染源的問題，生物偵測提供一個另外可行的方案，並可與環境暴露值建立彼此的關係。在此篇報告，經由單腔毒物動力學模式（PBTK），我們利用個體血液中毒物濃度隨時間測量值回推其環境暴露值。考慮質量不滅方程式所得的毒物動力學模式的隨機變異轉換而成的狀態空間模式（state-space model），模式的未知參數及環境暴露值可以利用 MCMC 模擬收斂後的樣本估計而得。所提出的方法在 styrene 暴露(Wang et al, 1996)的個案研究中表現良好，結果並顯示常在統計分析中被忽略的個體內在隨機變異，比起測量誤差變異有將近三倍之多。

關鍵詞：生物標記，動態線性狀態空間模式，Kalman 濾程，MCMC 模擬，人體毒物動力學模式，平穩分布

Classical environmental exposure assessment may suffer from poor quality of large variations in sampling sites and often difficulties in identifying the contamination sources. Biological monitoring measurements, as an alternative, may be obtained to relate with the environmental exposures instead. In this paper, we estimate individual (inhalation) exposure retrospectively from his (her) blood concentrations via a one-compartment physiologically-based toxicokinetic (PBTK) model. Considering stochastic variations to the mass-balance equation of the PBTK model, the solution to the resultant stochastic differential equation is transformed into a dynamic linear state-space model. Samples of the unknown model parameters and the mean inhalation concentration are then obtained via the MCMC simulations iteratively until convergence. We applied the proposed method to the analysis of the styrene data (Wang et al, 1996) to backward estimate the inhalation concentration assuming it is unknown. The result showed that the method performed well. Also, the data analysis showed that the internal variations, often ignored in population PBTK model analysis, outweighed in standard deviation three times of that of the measurement error.

KEY WORDS: Biomarker; Dynamic linear state-space model; Kalman filter; MCMC; PBTK model; Process error; Stationary.

報告內容

一、前言

Current U. S. Environmental Protect Agency risk assessment guidelines consist of four main parts: hazard identification, exposure assessment, dose-response assessment, and risk characterization. Among these steps, exposure assessment methodologies themselves not only interest environmental scientists, but the follow-up dose-response relationship between exposure to hazardous chemicals and the risks of disease is a major goal for occupational and environmental epidemiologists, and provides inferences for regulatory purposes. However, due to large variations in sampling sites and sometimes difficulties in tracing sources of hazardous substances, traditional assessments in environmental exposure often suffers from poor data quality.

二、研究目的

To accommodate the measurement problems in classical exposure assessment, some occupational health organizations such as the American Conference of Governmental Industrial Hygienists (ACGIH, 2001), the Deutsche Forschungsgemeinschaft (DFG, 2001) and the Japan Society for Occupational Health (JSOH, 2001) propose to evaluate the unmetabolized solvent in biological materials such as blood or urine as a marker of exposure to the solvent (Takeuchi, *et al*, 2002). Among these, biological exposure indices (BEIs), representing the biological levels from a worker being exposed to an airborne chemical at the threshold limit value (TLV), have been advocated to provide the same margin of safety as TLVs. The relationships between the biomarkers and the environmental exposure can then be explored to set the regulation limits. Assuming that the kinetic process is linear and the underlying environmental exposure is stationary, the relationship between accumulative exposure and biologically effective dose is strictly proportional. And thus biomarkers may serve as a surrogate and an indirect method of exposure assessment. Among other advantages, some biomarkers can substantially smooth the extreme variability in environmental toxicants exposure; biological monitoring accounts for all routes (inhalation, ingestion, and dermal absorption) and thus provides total individual exposure; and various biomarkers account for differences in uptake, elimination, and metabolism of toxic substances (Rappaport et al., 1995).

三、文獻探討

To establish the relationship between biomarkers and (occupational) exposure in standard statistical analysis, one usually analyzes appropriate biomarker concentrations from workers who have been exposed to a chemical and then fits a simple linear regression model. The obtained deterministic model, however, may fail to incorporate the stochastic nature in biomarkers for the whole study population (Crawford-Brown, 2000), in which, the true relationship is masked by inter-individual differences (Thomas et al., 1996). As an alternative, internal biomarker concentrations may be calculated and simulated by a PBTK model, for which the human body is subdivided into anatomical compartments representing individual organs or tissue groups to

account for inter-individual variations (Leung and Paustenbach, 1988; Leung, 1992; Perbellini et al., 1990; Thomas et al., 1996). The transfer of chemicals between the compartments is then described by mass balance differential equations incorporating the distributions of blood flows, partition coefficients, and tissue volumes (Thomas et al., 1996).

Though a population-based PBTK model is very useful in calculating stochastic biological concentrations, it involves many unknown model parameters that vary individually. Bois et al. (1996) successfully employed the Markov Chain Monte Carlo (MCMC) simulation techniques to simulate the PBTK model parameters from corresponding stationary distributions after convergence. Thus, statistical inferences on internal concentrations can be made based on the estimated model parameters. However, they considered only measurement errors for the biological measurements. Owing to the complexity of kinetic mechanism of human body, the internal stochastic variations within compartments may be more dominant than errors due to laboratory assessments.

Under dynamic state-space model, Chen et al. (2003) considered internal stochastic variations together with measurement error simultaneously to obtain the model parameters estimates similarly using the MCMC simulations. Overgaard et al. (2005) and Kristensen, Madsen and Ingwersen (2005) similarly applied stochastic differential equations (SDE) in PK/PD model development and parameters estimation. However, their results are mainly based on normal approximations to the solution of the SDEs and asymptotic properties of the maximum likelihood parameters estimates. For biological measurement studies, typically both the number of study subjects and times of measurements are very limited. Thus, asymptotic results may not be stable numerically.

四、研究方法

In this paper, based on a simplified one compartment PBTK model, we apply the methodology to estimate the unknown exterior exposure backwards from sampled blood concentration measurements. Assume for the present, that the route of chemical exposure is only through inhalation, and there is neither skin absorption nor oral intake. Since the study subjects are exposed to hazardous chemicals in their working environment, the internal concentrations among compartments are assumed to have reached equilibrium, and the whole body can be treated as a single compartment (Sato et al., 1974; Wang et al., 1996). Therefore, for our estimation purpose, a single compartment model would be fairly sufficient.

As an illustration, we reanalyzed the styrene exposure data of Wang et al. (1996). The original study purpose was to examine whether previous styrene exposure increases the human liver's metabolic ability. Here, we retrospectively estimate the underlying exposure from the volunteers' blood concentration measurements. The results showed that the proposed method estimated the true exposure reasonably well, and thus may be employed as an alternative to traditional environmental exposure assessment. Furthermore, the internal variations dominated much more than the measurement errors for this study. Therefore, analytical results on PBTK models based on pure measurement error assumption may need to be taken with care. Section 2 establishes the transformed state-space model of the one-compartment PBTK model. In Section 3,

we give the Bayesian framework to derive the unknown environmental exposure from measured blood samples. The MCMC algorithm is employed to simulate the unknown model parameters and environmental exposure distribution. We give the styrene data analysis and some simulations in Section 4. The last section discusses some further applications and concluding remarks.

五、結果與討論

For a group of subjects from a certain exposed population, the inhalation concentration C_{inh} is actually subject-specific and is different from time to time, rather than a time-independent constant. The estimated mean exposure level C_{inh} is therefore population–based, and is time-weighted average. Also, covariables such as job categories, working places, and time shifts can be introduced into a statistical model to estimate the exposures under different working environment, provided there are sufficient subjects with repeated biological measurements. For example, a log-linear model with vector of covariables **X** could be written as

$$\log C_{inh} = \mathbf{X}\boldsymbol{\beta},$$

and the mean C_{inh}'s could be estimated from measurements of subjects fallen within corresponding subcategories. The group difference in the styrene exposure example showed one such application.

As an application to the biological exposure indices BEIs corresponding to the TLV for regulatory purpose, the BEI is dynamic due to metabolic process, however, unless the internal system of the whole body has reached steady state (Chen et al., 2004b). Thus, there would be an ambiguity in the measurement time point. The proposed backward estimation of the environmental exposure provides an alternative as to whether exposure has exceeded regulatory TLVs. In addition to the point estimation of C_{inh}, the probability that C_{inh} is greater than TLV is

$$P(C_{inh} > TLV) = \int_{\{C_{inh} > TLV\}} f(C_{inh} \mid \mathbf{Z_m}, F_m) dC_{inh},$$

which can be approximated from the empirical posterior distribution $f(C_{inh} \mid \mathbf{Z_m}, F_m)$ of the adapted MCMC simulations.

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計畫成果自評

本研究計畫雖僅為期一年，但研究內容事實上已持續三年以上，其間所面臨最大的瓶頸在於必須自行撰寫一套繁複的電腦程式，以及無數的計算問題。基本上上述問題均已一一克服，並可應用在後續問題的研究上。本研究成果在相關領域應用上，有許多創新之處，預期將是一篇重要文獻。