SRA Dose-Response Specialty Group
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Development of practical quantifying method applicable for risk assessment of metabolic inhibition during co-exposure in workplaces by applying a PBPK model in humans

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The current understanding of occupational exposure of industrial chemicals along with supply chain process is that only a limited relevant data are available in Japan, although periodical health and indoor monitoring in workplaces has been carrying out for long years. And it is difficult to figure out the risk level such as how often concentrations of chemical substances exceed the administrative control level. Especially for downstream users of manufacturers that use chemicals, sometimes only a limited knowledge for chemical co-exposure are shared and thus relatively high exposure situations are realized in work place. Meanwhile, it is also known that some animal experiments for these representative chemicals have shown that the co-exposure of compounds causes the mutual metabolic inhibition through a competition for key metabolizing enzymes. They show that when chemical compounds interact at the same metabolic enzyme, blood concentrations of chemicals in test animals increase more than that single exposure (Yu et al, 1998). At present, chemical substances in workplaces were managed based on administrative control level for single substance. When a number of chemical substances are used in a workplace, they are managed on the assumption that risk (Hazard Index) increase additively. The Hazard Index is calculated as the sum of the ratio a chemical's exposure level to administrative control level, such that values larger than 1 are of concern. However the management based on this assumption cannot appropriately control compounds concerned the effect of metabolic inhibition. Therefore it remains to be elucidated that the effect of metabolic inhibition is quantified. It is important to develop the method to quantify the effect of the metabolic inhibition in order to support risk-based chemical management in occupational workplaces. Based on the above considerations, we aim to develop the method to quantify the effect of metabolic inhibition in order to support risk management in occupational workplaces. In particular, we construct the method to derive dose-response curve by applying PBPK model for the metabolic inhibition and assess the effect caused by co-exposure with the case of toluene and n-hexane which relatively have enough available information about mutual metabolic inhibition. Using the method to integrate the PBPK model applicable for co-exposure to toluene and n-hexane (Yu et al, 1998) into the hierarchical model to evaluate the dose-response relations by dividing into pharmacokinetics (PK) and pharmacodynamics (PD), we have derived the dose-response curve including metabolic inhibition. We did these analysis by the following algorism. (1) Construction of a PBPK model applicable for co-exposure of chemicals. (1-1) Programming a PBPK model including metabolic inhibition (Yu et al. 1998) in C language by using the Runge-Kutta method. (1-2) Comparing the estimated value by a PBPK model with measured value for validation of the PBPK model. (2) Derivation of dose-response curve for a single substance. (2-1) Integrating the data on two references evidenced about the standard value by ACGIH (TLV_TWA) by using meta-analysis. (2-2) Fitting the logistic model to these data. (3) Derivation of dose-response curve for co-exposure by using hierarchical model. (3-1) Estimating the internal dose from the external dose by using a PBPK model for a single substance or for co-

exposure. (3-2) Developing the relation between external dose and probability of a tumor (PD) for co-exposure by hierarchical model. (3-3) Fitting the logistic model to these estimated levels for co-exposure. In this research, two measures wereemployed as internal dose based on the results of Anna-Karin Mork, et al (2010): the 24-h area under the concentration time curve (AUC) and the maximum concentration of toluene in blood (C max). The hourly fluctuation of exposure and workload were also assumed by reference to Anna-Karin et al, (2010): the hourly fluctuation of exposure was set to be for 8 h, from 8:00-12:00 A.M. and from 1:00 to 5:00 P.M., and workload was considered light physical exercise of 50 W during work, a physical activity of 25 W during lunch break (12:00 A.M. to 1:00 P.M.) and in the evening after exposure, 0 at night (11:00 P.M. to 7:00 A.M.). As a result, estimated blood concentrations of toluene and n-hexane by a PBPK model for a single substance were in general agreement with the observed concentrations. Additionally, based on the dose-response curve derived by source of data, BMD10 corresponding to the TLV_TWA was obtained. Moreover, by quantifying the variation of risk levels such as BMD10 from the dose-response curve excluding metabolic inhibition and the curve including metabolic inhibition, the effect of the metabolic inhibition was quantified for every administered concentration of competing chemical substances. In this paper, we developed the method to quantify the effect of metabolic inhibition and quantify the extent of upward shift of dose-response curve for co-exposure in occupational workplaces with case of toluene and n-hexane. These results in this method provide a new quantitative knowledge for the mutual metabolic inhibition by co-exposure in workplaces. It can evaluate the threshold of co-exposure interaction for every the exposure level of the other substance exposed at the same time. Moreover, this method could be applied to another type of combination of chemicals which causes the mutual metabolic inhibition if their metabolic inhibition mechanism is clear. Therefore, for the further development of this method, we deem it necessary to classify compounds which may cause the mutual metabolic inhibition in workplaces, and to clarify the competition mechanism of metabolic enzyme.