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Determination of benchmark dose based on adduct and micronucleus formations in formaldehyde-exposed workers

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1. Introduction

Formaldehyde which is widely used as ingredient or adhesive for wood and glass products is also classified as a carcinogen for nasopharyngeal cancer (Cogliano et al., 2005) and leukemia (Nielsen et al., 2017). Therefore, the American Conference of Governmental Industrial Hygienists, for example, has set a short-time exposure limit of 0.37 mg/m^3 (ACGIH, 2019). However, these standards are determined mainly based on using the no-observed-adverse-effect-level (NOAEL) approach in experimental animals (Ringblom et al., 2014) which would benefit from confirmation via human studies.

During the recent decades, China has become the largest formaldehyde producer and consumer in the world (Tang et al., 2009). Consequently, the Chinese government has also established guidelines to reduce occupational formaldehyde exposure but their value in reducing health hazards has not been determined yet. Therefore, for the protection of workers in China and around the world, the use of a more stringent exposure limit, such as the benchmark dose (BMD), will be helpful.

BMD is a statistical lower confidence limit for a dose which would produce some predetermined increase in response rates (1–10%) (Crump, 1984). Unlike using the NOAEL protocol which ignores the lowest level dose-response relationship, the BMD method consider the entire dose-response curve for fitting into mathematical models (Lin and Tai-yi, 2007). It also provides the calculation of the lower 95% confidence interval of BMD, BMDL, which shows consideration of uncertainty.

Previous studies demonstrate that formaldehyde in the blood can bind human serum albumin covalently and form formaldehyde-albumin adducts (FA-HSA) (Thrasher et al., 1990). This special adduct can be used as a biological marker for identification of formaldehyde exposure (Carraro et al., 1999). Furthermore, formaldehyde can cause DNA damage which can be identified in peripheral blood cells, e.g. DNA strand breaks (Zendehdel et al., 2018), micronuclei and chromosome damage (Zhang et al., 2010; Zhang et al., 2009), in dose-response effects (Marcon et al., 2014). However, these biomarkers have not been used efficiently to estimate BMD for formaldehyde exposure (Lin et al., 2013; Liu et al., 2017).

In this study, 100 formaldehyde-exposed workers were selected and matched with 100 controls. The objective was to determine the BMD using the cumulative exposure dose (CED) as external exposure measurement, serum FA-HSA as internal exposure measurement and MN as health hazard assessment.

2. Materials and methods

2.1. Exposed and control subjects

The study was approved by the Ethics Committee of the Fudan University and all subjects provided written informed consent before their participation in the study. Formaldehyde-exposed workers were recruited from a chemical factory in Shanghai, China. Questionnaires were administrated by trained field researchers to collect information about demographic characteristics, smoking status, alcohol use, medical history and occupational history, including job types and numbers of work years. A total of 100 male workers who had been exposed to formaldehyde for more than 1 year were recruited as the exposed group. In addition, 100 male non-exposed workers from the same factory were matched by age to the exposed workers and were recruited as the control group. All subjects completed the questionnaire and donated blood samples.

2.2. Exposure assessment

Exposed workers were recruited from 4 different work conditions in the factory: production examination, glue spraying, coating and

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workplace inspection. Moreover, the factory regularly conducted formaldehyde monitoring (Formaldemeter htV, PPM Technology Ltd, UK) to estimate air formaldehyde concentrations in the designate sample sites according to the China national standard: *Specifications of Air Sampling for Hazardous Substances Monitoring in the Workplace* (GBZ 159–2004).

2.3. Assessment of formaldehyde exposure

By inputting the monitored data into our standardized methods (Wang et al., 2013; Zheng et al., 2017), the cumulative exposure dose (CED) for each worker was determined using the following equation:

$$\mathrm{CED}(mg/m\hat{}3 - year) = \sum C\,(mg/m\hat{}3) \times T\,(year)$$

where *C (mg/m^3)* is the geometric mean of formaldehyde exposure concentration for a year in a given workplace. *T (year)* is the number of work years.

2.4. FA-HAS determination

During the field study, fasting venous peripheral blood samples (2 ml) were drawn by physicians using coagulant vacuum tubes, then rapidly centrifuged and stored at −80°C before analysis. The determination of serum FA-HSA concentrations was conducted using human FA-HSA enzyme-linked immunoassay kit (R&D systems, Minnesota, USA) according to the manufacturer's instructions.

2.5. CBMN assay

The cytokinesis-blocked MN (CBMN) assay was performed according to standard methods as described in our previous study (Qiu et al., 2011). Briefly, 0.5 ml heparinized venous peripheral blood was transferred to 4.5 ml cell culture medium and incubated under 37 °C for 44 h. Then, 6 μg/ml Cytochalasin-B (Sigma-Aldrich, St. Louis, MO, USA) was added to the cultures. Cells were harvested 28 h later and fixed with a mixture of methanol and acetic acid solution (3:1). Slides were air-dried, stained with Giemsa and scored for CBMN, as the number of MN observed per 1000 lymphocytes, expressed as a count per thousand (‰).

2.6. Statistical analysis

Exposure measurement and MN data were linked for each subject. Shapiro-Wilk test was conducted to examine the normality of the included variables. Comparisons between the control and exposed groups for subject characteristics (age, smoking status and alcohol use) were performed using the Mann-Whitney test. Due to the non-normal distribution of MN frequency, ANOVA was used to test the difference between groups with age, smoking status and alcohol use as covariates. Correlations between CED and serum FA-HSA concentrations were analyzed using multivariate regression analysis with age, smoking status and alcohol use as covariates.

To further confirm the dose-response relationship between formaldehyde exposure and MN frequency, the total study population were subdivided into four groups by the quartile cumulative dose (0.01–0.06 mg/m^3, 0.06–0.125 mg/m^3, 0.125–0.9 mg/m^3, 0.9–3.75 mg/m^3) and the quartile FA-HSA concentration (3.65–17.90 ng/ml, 17.90–21.78 ng/ml, 21.78–27.93 ng/ml, 27.93–69.54 ng/ml). Multivariate Poisson regression analysis was performed to examine the relationship between CED/FA-HSA and MN frequency. The risk of MN formation was estimated by calculating the frequency ratios (FR = e^{β}, β: regression coefficient): an increase in FR would suggest proportional change of MN compared to the control group. The statistical tests were two-sided, and values of $p < 0.05$ were considered statistically significant. All models mentioned above were performed using R software (Version 3.5.1, R Foundation for Statistical Computing, Vienna, Austria).

2.7. Benchmark dose estimation

After confirming the dose-response relationships between formaldehyde exposure and MN frequency, Benchmark Dose Software (BMDS) Version 2.7 (U.S. EPA) was used for calculating BMD and its 95% lower confidence limit, BMDL. Since, there was no acceptable limit based on MN frequencies, a threshold limit was adopted which was the 95 percentile of the controls' MN frequency (3‰) to dichotomize MN frequency of total subjects into a binary variable, named: chromosome damage (Wang et al., 2013; Niu et al., 2018). The BMD was determined as the dose at which exposure would result in a specified level of increase in adverse response compared to that of the control. This specified level of increase in adverse response is called benchmark response (BMR) level, which was considered here as the 10% additional risk above the background. In addition, different dichotomous dose-response models were performed to test the fitness of these correlations. These models would be selected for use according to their Akaike Information Coefficient (AIC) and *p* values.

The BMD value was also calculated by using the MN frequency as the continuous variable. The BMR was defined as the background estimate plus the standard deviation for the control group data. The various dose-response continuous models were also performed to test the fitness and selected according to their AIC values and biological plausibility. However, for comparison with previous studies (Zheng et al., 2017; Niu et al., 2018; Wang et al., 2013), we demonstrated the BMD values estimated by dichotomous response models in the following text while the results from the continuous response models are presented in the supplemental material.

3. Results

3.1. Characteristics of the study subjects

Characteristics of the control and exposed workers are summarized in Table 1. Between the two groups, there was no significant difference for age, smoking status and alcohol use. However, the exposed workers had significantly longer employment duration as well as higher CED and FA-HAS level than those from the controls ($p < 0.001$). Due to the non-normal distribution of the health-related variables, non-parametric tests were conducted using age, smoking status and alcohol use as covariates. The results showed that the exposed workers had significant

Table 1
General characteristics, exposure levels and biological effects of the studied subjects.

	Control	Exposure	*p*
General Characteristics			
Age, year	35.5 ± 6.8	37.1 ± 7.2	0.244[a]
Smoking Status (yes, no)	41	47	0.395[b]
Alcohol use (yes, no)	17	21	0.473[b]
Work duration, year	6 (2, 10)	9 (6, 11.5)	< 0.001[a]
Exposure assessment			
CED, mg/m^3-year	0.06 (0.02, 0.10)	0.90 (0.60, 1.78)	< 0.001[a]
FA-HSA, ng/ml	19.59 (15.51, 23.04)	26.52 (20.68, 32.82)	< 0.001[a]
Health effects			
WBC	6.48 ± 1.63	5.99 ± 1.41	0.166[c]
NEU	3.78 ± 1.28	3.27 ± 1.01	0.092[c]
LYM	2.11 ± 0.58	2.13 ± 0.56	0.955[c]
MN frequency (‰)	1.71 ± 0.96	3.05 ± 1.47	< 0.001[c]

CED: cumulative exposure dose. FA-HSA: formaldehyde-albumin adduct. WBC: number of white blood cell. NEU: number of neutrophil. LYM: number of lymphocyte. MN: micronucleus.

[a] Calculated by using the Wilcoxon nonparametric analysis.

[b] Calculated by using the X^2 test.

[c] Calculated by using the Poisson regression models with adjustment for age, smoking status and alcohol use.

Table 2
Ambient formaldehyde (FA) concentrations, number of workers and samples collected in the five workshops.

Sampled Workplaces	Number of workers	Ambient FA concentrations (mg/m^3)		National Standard (mg/m^3)
		Range	Geometric Mean	
Production Examination	18	0.01–0.15	0.06	0.5
Glue Spraying	30	0.2–0.49	0.25	
Coating	28	0.067–0.15	0.1	
Workplace Inspection	24	0.05–0.2	0.09	
Logistics Workshop	100	0–0.01	0.01	

higher MN frequency than the controls but there was no difference in cytometry parameters.

Multivariable regression model was performed to test the consistency between CED and serum FA-HSA measurements. Age, smoking status and alcohol use were included into the model and forward-stepwise method was used for the selection. The analyses showed that the relationship between individual CED and serum FA-HSA was statistically significant ($\beta = 7.53$, $p < 0.001$) indicating that serum FA-HSA can be used as an internal exposure biomarker for external occupational exposure. The scatterplot for CED and serum FA-HSA is shown in Fig. S1.

3.2. Formaldehyde exposure assessment

Table 2 shows the ambient formaldehyde concentrations at the five workshops. The formaldehyde concentrations for the exposed workers ranged from 0.01 mg/m^3 to 0.49 mg/m^3, which did not exceed the China national standard for occupational exposure (0.5 mg/m^3). In addition, the samples collected from the logistic workshop contained less formaldehyde than at other workshops.

3.3. Formaldehyde exposure and MN frequency

To further investigate the relationships between formaldehyde exposure and MN frequency, all participants were sub-divided into four groups by the quartile cumulative dose (CED). As showed in Table 3, FR (95%CI) increased from 1.38 (1.00, 1.91), 1.83 (1.34, 2.52) and to 2.67 (1.99, 3.64) for increased CED level, respectively. There was also corresponding increases in FA-HAS as well as MN frequencies. A clear dose-response relationship was observed between FA-HSA concentrations and MN frequencies. Furthermore, the dichotomized MN frequencies of total subjects as a binary variable (Table 4) showed a trend in the Spearman correlation analyses ($R^2 = 0.59$, $p < 0.001$) (data not shown).

Table 4
Trend test for chromosome damage at different exposure levels in total subjects.

	Exposure Group (Range)	Normal	Damage	p[a]
CED, mg/m^3-year	0.01–0.06	41	4	< 0.001
	0.06–0.125	40	15	
	0.125–0.9	25	21	
	0.9–3.75	11	43	
FA-HSA, ng/ml	3.65–17.90	48	2	< 0.001
	17.90–21.78	34	16	
	21.78–27.93	30	20	
	27.93–69.54	5	45	

CED: cumulative exposure dose. FA-HSA: formaldehyde-albumin adduct. Chromosome damage was defined as micronucleus frequency ≥3‰.
[a] Calculated by using the Spearman correlation test.

3.4. Determinations of BMD based on dose-response of chromosomal damage prevalence

The BMD model was selected for use among the six dichotomous model according to the AIC and p values. Considering the smaller AIC value, the better goodness-of-fit and the global measurement of model fitness required p value no less than 0.1. Our data suggested the use of the log-logistic model to perform the BMD analysis for CED variable and the Gamma model for FA-HSA (Table 5).

From the fitted dose-response model, the BMD of formaldehyde cumulative exposure dose was 0.067 mg/m^3-year (BMDL: 0.042 mg/m^3-year) (Fig. 1). The BMD of FA-HSA concentration was 16.13 ng/ml, the BMDL was 14.24 ng/ml (Fig. 2).

4. Discussion

Formaldehyde has been classified as a human carcinogen (IARC, 2006), however, there have not been sufficient reports that demonstrate how inhaled formaldehyde reaches sites distant to the site of initial contact following inhalation exposure (Swenberg et al., 2013). Also, mechanisms for leukemogenesis have not been systematically characterized therefore assessment of risk has not been precise (Zhang et al., 2010). Among several acceptable hypothesized mechanisms, one is the formation of DNA-protein cross-links (DPC) which would lead to DNA strand breaks, cell division errors, MN formation and initiation of carcinogenesis. Our systematic study was conducted to investigate such a mechanism and to identify the BMD for improved assessment of health risk. From our knowledge, this is the first report on determination of BMD which was based on serum FA-HAS levels and other measurements in exposed workers.

Besides occupational exposure, individuals can also be exposed to formaldehyde from consumption of a variety of food and alcoholic beverages. Indeed, formaldehyde intake may range from 1.5 to 14 mg per person per day (Feron et al., 1991). Therefore, alcohol consumption was entered into our multivariate analysis and the analysis did not change the significant association between occupational formaldehyde-

Table 3
Differences in micronucleus (MN) frequencies from formaldehyde (FA) exposure.

	Exposure Group (Range)	Number	MN Freq ± SE(‰)	FR (95%CI)[a]
CED, mg/m^3-year	0.01–0.06	45	1.36 ± 0.86	1
	0.06–0.125	55	1.87 ± 0.92	1.38 (1.00, 1.91)
	0.125–0.9	46	2.50 ± 1.17	1.83 (1.34, 2.52)
	0.9–3.75	54	3.65 ± 1.40	2.67 (1.99, 3.64)
FA-HSA, ng/ml	3.65–17.90	50	1.22 ± 0.76	1
	17.90–21.78	50	2.06 ± 0.79	1.68 (1.23, 2.32)
	21.78–27.93	50	2.32 ± 1.04	1.89 (1.39, 2.60)
	27.93–69.54	50	3.92 ± 1.35	3.20 (2.39, 4.33)

CED: cumulative exposure dose. FA-HSA: formaldehyde-albumin adduct. MN: micronucleus. FR: frequency ratio, compared with the pooled control group.
[a] Calculated by using the multivariate Poisson regression models with adjustment for age, smoking status and alcohol use.

Table 5
Different models used to estimate the bench-mark dose and level (BMD and BMDL) for two biomarkers of formaldehyde (FA) exposure for all subjects.

	Model	BMD	BMDL	AIC	*p*
CED, mg/m^3-year	Gamma	0.132	0.1002	217.101	0.1736
	Logistic	0.28976	0.2363	220.833	0.037
	Log-logistic	0.0666	0.0419	215.998	0.2761
	Probit	0.2831	0.2362	220.72	0.0384
	Quantal-linear	0.132	0.1002	217.101	0.1736
	Weibull	0.132	0.1002	217.101	0.1736
FA-HSA, ng/ml	Gamma	16.1263	14.2435	186.505	0.1949
	Logistic	15.52	13.2112	187.39	0.1317
	Log-logistic	16.2747	14.408	187.314	0.1303
	Probit	15.5688	13.2004	186.775	0.1746
	Quantal-linear	4.2638	3.56197	228.604	< 0.001
	Weibull	15.4218	13.3264	186.623	0.1914

CED: cumulative exposure dose. FA-HSA: formaldehyde-albumin adduct. AIC: Akaike Information Criterion values, the smaller the value is, the better the model fits.

cumulative exposure and MN. Our observation is supported by Monakhova's study which shown that the cancer risk from formaldehyde to the alcohol-consuming population is negligible (Monakhova et al., 2012).

Although the occupational formaldehyde concentrations in our study were much lower than the national standard in China, the exposed workers did show significant higher MN frequencies than that of the controls, as well as dose-response relationships, which is consistent with other studies (Lin et al., 2013). In addition, Lin's study shown that MN frequencies was significantly associated with the number of work years but not with real-time exposure which suggest that the MN frequencies might reflect cumulative damage from chronic exposure. Consistent with such observation, our study indicates a significant dose-response relationship between the MN frequencies and cumulative formaldehyde exposure.

To further determine exposure limits based on biological evaluations, the BMD and BMDL of the CED, and serum FA-HSA were calculated using appropriate models. By comparing the AIC values, where smaller values would indicate better fitness, the log-logistic model was used to conduct the BMD analysis for CED and the Gamma model for FA-HSA. In addition, the *p* value which represents the global measurement of model fitness, was recommended to be no less than 0.1, which can also be satisfied in these two models. From the fitted model, the BMD of formaldehyde cumulative annual exposure dose was 0.067 mg/m^3 (BMDL: 0.042 mg/m^3). These data suggest that the current exposure limit in China may not be adequate in preventing health hazards for workers or for the public.

From our review of the literature, only one recent study was similar to ours and the study provided the BMD level of 0.107 mg/m^3 (BMDL: 0.038 mg/m^3) based on the study of formaldehyde cumulative exposure dose in Iranian workers (Zendehdel et al., 2018). Their BMD value was higher and with wider confidence intervals than ours. A careful comparison of our two papers indicates that the experimental approaches were vastly different which might explain the difference in the two observations. First, the former study used 53 exposed and 34 control subjects whereas our sample size was much bigger which should give us more statistical power (100 exposed workers and 100 controls). The exposed workers in the former study came from a melamine dinnerware industry with co-exposure to melamine which is highly toxic (Bolden et al., 2017) whereas ours come from a chemical factory with formaldehyde being the major toxic chemical. For exposure dosimeter, the former set the control level at 0 whereas we conducted actual measurements which would reduce the bias caused by exposure misclassifications. Also, the participants in our study were all male workers while the Iranian study contained several female workers. Although this would limit the extrapolation of our results only to male workers, it could eliminate the potential bias introduced by having different genders. More importantly, the former one used the less reliable DNA strand break Comet assay than our MN assay for hazard assessment (Kirsch-Volders et al., 2018; Norppa, 1997). This difference in endpoint modeled could also cause heterogeneity in the concluded BMD value.

Previous studies (Pala et al., 2008; Vecchio et al., 2004) suggest that serum FA-HSA could be a biological marker for recent or peak formaldehyde exposure. For example, Pala's study observed significant correlations in serum FA-HSA among workers occupational exposed to real-time formaldehyde level (Pala et al., 2008). However, they did not find any significant trend change between effective biomarkers (micronuclei, chromosome aberrations and sister chromatid exchanges) and formaldehyde level while we found a dose-response relationship between CED/FA-HSA and MN frequency. Since the factory's record indicates that the formaldehyde concentrations have been lower than the national standard and had been steady during our study period, the serum FA-HSA level here may also demonstrate the association with cumulative exposure. In addition, formaldehyde is widely known to cause extensive adverse effects at the portal of entry. Although previous

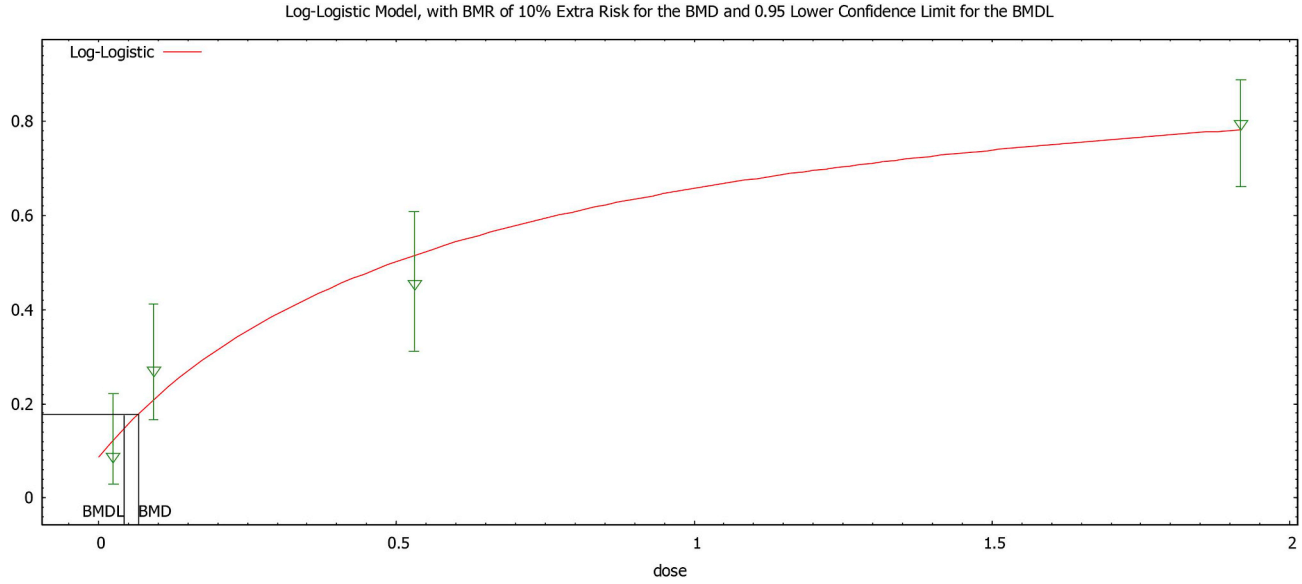

Fig. 1. Use of the Log-logistic model to estimate the bench-mark dose and level (BMD and BMDL) for cumulative formaldehyde exposure (CED, mg/m^3-year).

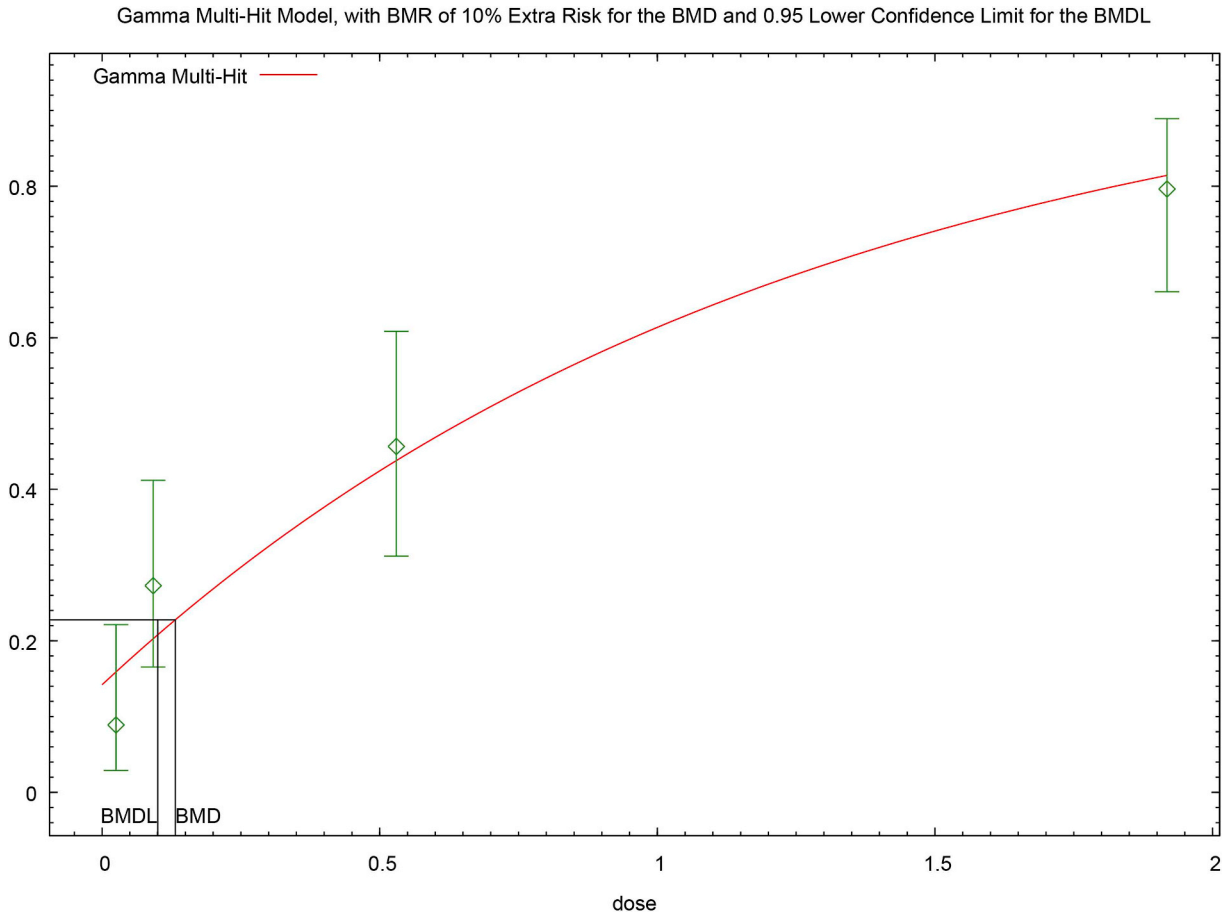

Fig. 2. Use of the Gamma model to estimate the bench-mark dose and level (BMD and BMDL) for formaldehyde-albumin adduct (FA-HSA, ng/ml).

research suggested that it might enter the systemic circulation (NTP, 2010), the degree to which it reached the blood is still controversial. Besides, since formaldehyde is also formed endogenously, it is not clear that serum FA-HSA levels are a measure of external inhalation exposure. Recently, Liu's study demonstrated a new quantification method that could detect endogenous and exogenous DPC levels in HEK293T cell treated with labeled formaldehyde which could facilitate the understanding of the mechanisms for formaldehyde-induced DPC repair (Liu et al., 2018). Overall, as the first one that estimated the BMD value of serum FA-HSA in occupational workers, our study should be accepted with caution and more studies are needed to test its feasibility.

It should be stated that the use of MN formation cannot be considered as the specific biological effects from formaldehyde exposure because MN can be induced by other environmental mutagens (Kirsch-Volders et al., 2018). Besides, unlike animal experiments which could calculate the BMD value by using tumor prevalence as endpoint, the population study usually use pre-carcinogenic lesions such as the formation of DNA-protein cross-links (Zendehdel et al., 2018) or MN (Niu et al., 2018) as response indicator. These non-disease-specific biomarkers tend to be more sensitive and appear earlier than the actual initiation of carcinogenesis. These may contribute to our lower BMD value than other studies.

5. Conclusions

Our study indicates that current occupational exposure to formaldehyde increased MN frequencies and therefore increased health risk in workers in China. In addition, the BMD value of CED was lower than the current China national standard which further suggests that the current exposure standard might not be adequate. Therefore, our identified BMD can be used with other data to further reduce the potential health hazards caused by occupational formaldehyde exposure.

Conflicts of interest

The authors report no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2019.05.008.

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