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Feasibility of using urinary TDGA as a biomarker for VCM exposures☆

Chao W. Chen[a,b,*], Dennis Hsieh[c], Fung-Chang Sung[d], Shan P. Tsai[e]

[a] University of Maryland University College, Adelphi, MD, USA
[b] National Center of Environmental Assessment, US Environmental Protection Agency, Washing, D. C, USA
[c] Department of Environmental Toxicology, University of California, Davis, CA, USA
[d] Department of Health Service Administration, China Medical University, Taichung, Taiwan
[e] Texas A&M, School of Public Health, College Station, TX, USA

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ABSTRACT

Thiodiglycolic acid (TDGA) is a major metabolite of vinyl chloride monomer (VCM), and it has been suggested as an exposure biomarker for VCM. The validity of this biomarker when the level of VCM is less than 5 ppm, however, is questionable. The objective of this article is to evaluate the feasibility of using urinary TDGA as a biomarker of VCM exposure in a community health risk assessment setting where the concentration of VCM in air is typically very low (likely below 1 ppm). To achieve this objective, we examine the fraction of urinary TDGA associated with different levels of VCM exposures of three studies from different countries, using estimations of the TDGA metabolite predicted by a PBPK model. It is demonstrated that differences in background TDGA have considerable effect on the adequacy of TDGA as a biomarker of VCM. We conclude that, in a community health assessment setting, TDGA should not be used as an exposure biomarker for VCM without having a proper control group, and a PBPK model can be used first to determine whether or not the amount of TDGA in urine is of concern.

1. Introduction

Thiodiglycolic acid (TDGA) in urine is a major metabolite of vinyl chloride monomer (VCM), and it has been a subject of extensive research interest worldwide (Muller et al., 1978; Heger et al., 1982; Navratil et al., 2004; Cheng et al., 2001). Urinary TDGA has been considered a useful biomarker for VCM exposure because it is more stable and has a longer half-life than VCM, and accounts for about 50% of total metabolites after a VCM exposure (Watanabe et al., 1976; Muller et al., 1978; Lei et al., 2014). Given the difference in background TDGA levels among study populations, it is questionable whether urinary TDGA can be used as an exposure biomarker when the level of VCM is less than 5 ppm in the air. It is well recognized that urinary TDGA can be attributed to factors other than VCM exposure; therefore, it is necessary to consider background TDGA. In their search for normal (background) values of TDGA level in urine of healthy persons, Navratil et al., 2004 found that TDGA can be significantly elevated because of dietary and/or supplement intakes (e.g., consumption of fresh onion and other root vegetables containing s-carboxymethyl-L-cysteine, after drinking certain alcohol beverages, after an intake of vitamin B_{12}, or undergoing treatment of allergy to pollen with cetirizine). On the basis of 55 healthy persons of both genders from the Czech Republic, Navratil et al., 2004 found that the TDGA concentration in urine amounts to 14.9 ± 2.6 mg/L, or 15.4 ± 3.5 mg/g Cr (mean ± standard deviation) where Cr represents urinary creatinine. The background TDGA in urine varies greatly among studies that are the only available studies with adequate data for investigation (Muller et al., 1978; Heger et al., 1982; Navratil et al., 2004; Cheng et al., 2001). Cheng et al. (2001) suggests that urinary TDGA can be used as an exposure biomarker for VCM only when the concentration of VCM exceeds 5 ppm in the air, while other studies (Muller et al., 1978; Heger et al., 1982) suggest that the urinary TGDA can be used as a VCM exposure biomarker even when VCM is less than 5 ppm in air. From the view point of VCM exposures, an observation of urinary TDGA consists of two components: signal (VCM-derived TDGA), and noise (non VCM-derived TDGA). Therefore, an analysis of the signal to noise ratio, or its equivalent indices such as the fraction of the signal to be defined later, becomes essential for determining the potential VCM exposures in a community health risk assessment. The signal component in an observed urinary TDGA level cannot be readily estimated because the background TDGA concentration is not a constant. The aim of this article is to analyze the available data to clarify the conflicting conclusions about the usability of the urinary TDGA and suggest an appropriate strategy of using it as an exposure biomarker when VCM air concentration, if it exists, is small.

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* Corresponding author. University of Maryland University College, Adelphi, MD, USA.
E-mail address: chao.chen@faculty.umus.edu (C.W. Chen).

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Table 1
Individual VCM Level in Air, along with Observed and PBPK Predicted TDGA in Urine, based on Heger et al. Study.
Source: Heger et al., 1982. Data are reproduced from Fig 4, Heger et al., 1982, by a digitizer.

Subject	VCM, ppm	Urinary TDGA, mg/24 h.	PBPK Predicted TDGA*, mg/24 h.	
			Clewell et al., 2001	Chen and Blancato, 1989
1	1.263	1.356	0.620	0.782
2	2.155	3.925	1.058	1.355
3	2.375	3.417	1.165	1.469
4	2.475	3.930	1.214	1.531
5	5.911	7.766	2.896	3.653
6	9.216	7.870	4.505	5.692
7	14.653	13.730	7.139	9.030
8	14.674	9.234	7.149	9.043

Our approach to achieve this objective is by breaking down the fraction of the signal in observations at different VCM exposure levels from three studies where both VCM concentration and urinary TDGA are available, utilizing the information of the total metabolites predicted by a PBPK model of VCM that is one of the most modeled compounds in risk assessment (Chen and Blancato, 1989; Barton et al., 1995; Reitz et al., 1996; Clewell et al., 2001). Studies from Heger et al. (1982), Cheng et al. (2001), and Navratil et al. (2004) will be used for the signal fraction analysis, while Muller et al. (1978) will serve as an example to illustrate the importance of having a control group in a community health study.

2. Data and method

2.1. Data available for investigations

Data from three studies (Tables 1–3) that represent workers from Germany (Heger et al., 1982), Taiwan (Cheng et al., 2001), and the Czech Republic (Navratil et al., 2004), are used as a basis for exploring the relationship between VCM exposures and TDGA in urine. These are the only studies identified from a literature search using a Google Scholar with combination of key words: thiodiglycolic acid, TDGA, vinyl chloride, VCM, human, and workers. All the subjects worked in plants manufacturing polyvinyl chloride (PVC) and other substances utilizing VCM. These studies provide information on VCM concentrations obtained by personal air sampling, and the corresponding TDGA in urine, expressed in mg/day, mg/l, or mg/g Cr. Data in Table 1 from Heger et al. (1982) represent the best data for studying the relationship between urinary TDGA and VCM exposures because the observations are less influenced by non-VCM factors. With help of the company physicians who followed strict criteria, 15 workers were recruited to take part in the study. The participants were given detailed instructions, advising them to avoid using anything (including shampoo use) that may influence the induction of TDGA in urine. Only 8 (out of 15) who had relatively long-term (longer than 5 min for each episode) exposures (labeled LE in Fig 4 in Heger al, 1982) are included in Table 1 for analysis. Because the workers in Heger et al. (1982) were advised to abstain from using anything that may influence the TDGA induction, the observed urinary TDGA values are expected to be less influenced by non-VCM factors than the other two studies. Data in Table 2 are reproduced from Cheng et al. (2001), estimated by combining end of shift and start of shift values. Cheng et al. (2001) also provides a linear relationship $Y = 1.06 + 0.57X$ for the urinary TDGA, Y, in mg/g Cr, and VCM, X, in ppm, with a caveat that the equation is applicable only for $x \geq 5$ ppm. This equation implies a high significance of background TDGA; for instance, at 1 ppm, the VCM-derived TDGA accounts for less

Table 2
Individual VCM Level in Air, along with Observed and PBPK Predicted TDGA in Urine, based on Cheng et al. Study.

Subject	VCM in Air (TWA, ppm)	TdGA in Urine, mg/24 h[a]	PBPK Predicted TDGA, mg/24 h.	
			Clewell et al., 2001	Chen and Blancato, 1989
1	0.05	13.63	0.022	0.030
2	0.10	2.67	0.048	0.061
3	0.17	2.74	0.083	0.104
4	0.25	0.88	0.123	0.155
5	0.58	1.72	0.285	0.359
6	0.68	0.43	0.335	0.421
7	1.11	3.56	0.545	0.687
8	2.23	2.74	1.094	1.381
9	2.91	18.29	1.427	1.800
10	3.39	1.86	1.663	2.097
11	4.03	11.58	1.976	2.495
12	4.86	3.49	2.382	3.007
13	5.59	6.71	2.739	3.206
14	8.17	3.08	3.997	5.485
15	12.08	6.64	5.893	7.452
16	13.38	17.81	6.524	8.249

Source: Cheng et al., 2001.
[a] Cheng et al. (2001) provides TDGA data for end of shift and start of shift, in mg/g Cr. The total TDGA, mg/d is calculated by 1.37*(end of shift + start of next shift)/2, where 1.37 is the converting factor used to convert unit from mg/g Cr. to mg/d.

Table 3
Individual VCM Level in Air, along with Observed and PBPK Predicted TDGA in Urine, based on Navratil et al. Study.
Source: Navratil et al., 2004.

No	VCM, ppm[a]	TDGA[b] (mg/24 h)	PBPK predicted TDGA, mg/24 h.	
			Clewell et al., 2001	Chen and Blancato, 1989
1	0.004	25.2	0.001	0.002
2	0.078	27.3	0.038	0.048
3	0.585	26.7	0.288	0.360
4	0.664	55.6	0.326	0.408
5	0.664	65.2	0.326	0.408
6	0.664	55.8	0.326	0.408
7	0.703	60.8	0.345	0.433
8	1.484	4.2	0.728	0.917
9	1.718	36.7	0.844	1.064
10	1.718	33.4	0.844	1.064
11	4.609	95.6	2.260	2.850
12	7.421	43.7	3.632	4.588
13	11.953	147.0	5.833	7.376

[a] Original unit in mg/m^3 but converted to ppm by the relationship 1 ppm = 2.56 mg/m^3.
[b] Day cumulative; original unit in mg/l but converted to mg/d, assuming the urine volume of 1 l/d.

Table 4
Signal fraction, f, Calculated from Table 1.

Subject	VCM, ppm	100 x f, Signal fraction in %	
		Clewell et al., 2001	Chen and Blancato, 1989
1	1.263	45.76	57.67
2	2.155	26.96	34.01
3	2.375	34.11	42.99
4	2.475	30.89	38.97
5	5.911	37.29	47.04
6	9.216	57.25	72.32
7	14.653	51.60	65.77
8	14.674	77.42	97.94

The fraction of signal in Table 4 ranges from 27% to 77%, and 34%–98% respectively when models of Clewell et al., and Chen and Blancato are used.