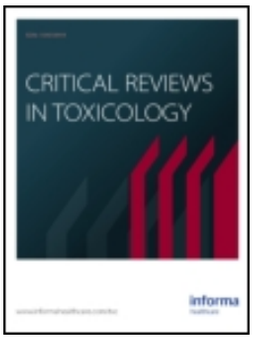

Critical Reviews in Toxicology

ISSN: 1040-8444 (Print) 1547-6898 (Online) Journal homepage: informahealthcare.com/journals/itxc20

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To cite this article: Feng Ru Tang & Weng Keong Loke (2013) Sulfur mustard and respiratory diseases: Revisit with special reference to the "Comments on 'Sulfur Mustard and Respiratory Diseases', Tang and Loke () and a prepared Integrated Mechanism for Chronic Pulmonary Disease from Exposure to Sulfur Mustard" by Saburi and Ghanei (), Critical Reviews in Toxicology, 43:3, 277-281, DOI: 10.3109/10408444.2013.764843

To link to this article: https://doi.org/10.3109/10408444.2013.764843

Published online: 12 Feb 2013.

Critical Reviews in Toxicology

http://informahealthcare.com/txc
ISSN: 1040-8444 (print), 1547-6898 (electronic)

Crit Rev Toxicol, 2013; 43(3): 277–281
© 2013 Informa Healthcare USA, Inc. DOI: 10.3109/10408444.2013.764843

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LETTER TO THE EDITOR

Sulfur mustard and respiratory diseases: Revisit with special reference to the ''Comments on 'Sulfur Mustard and Respiratory Diseases', Tang and Loke (2012) and a prepared Integrated Mechanism for Chronic Pulmonary Disease from Exposure to Sulfur Mustard'' by Saburi and Ghanei (2013)

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Dear Editor

We have read with some interest the comments by Saburi & Ghanei (2013) on our recent publication entitled ''Sulfur mustard and respiratory diseases'' (Tang & Loke, 2012) published in *Critical Reviews in Toxicology*. Here are our replies to their concerns.

Treatment of chronic phase respiratory effects

In Section 5.2. ''HD-induced chronic damages'', pp. 696–697, we have elaborated possible mechanisms involved in pathogenesis of mustard-induced chronic respiratory disease. Based on experimental data provided by various research groups, we have also mentioned at least six potential drug targets that could lead to a treatment solution for chronic phase respiratory effects (Tang & Loke, 2012). While highlighting these possible therapeutic approaches, it is important to note that most of the available clinical data (Ghanei et al., 2004, 2005, 2006, 2007; Panahi et al., 2005) were obtained from non-Randomized Clinical Trials (RCT), which has limited sample sizes, lacked case controls and double-blind randomized trial designs. Moreover, the amount of inhaled sulfur mustard toxicant in these case subjects were unknown, which complicate efforts in deriving a dose–response relationship. As preclinical studies on chronic phase respiratory diseases induced by sulfur mustard are still in early investigation phases, the authors are of the opinion that it is premature and potentially counter-productive to emphasis on any particular drug target at this stage. Further studies on both small and large animal models are clearly needed to provide more scientific data before any efforts are made in narrowing-down possible drug targets to derive a therapeutic solution.

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Pulmonary fibrosis and survival of patients

We have carefully read the two publications by Ghanei et al. (2008), Ghanel & Harandi (2007) and relevant references (Bjoraker et al., 1998; Costabel & King, 2001), and would like to highlight the following observations:

- In Bjoraker's paper, a median survival of 3 to 5 years was reported for patients with idiopathic pulmonary fibrosis (IPF), which may not be applicable to victims suffering from mustard-induced secondary pulmonary fibrosis (SPF) as reported by Emad & Rezaian (1997, 1999). Taghaddosinejad et al. (2011) recently studied gross and microscopic pulmonary lesions in cadavers and also assessed the main causes of mortality caused by mustard gas exposure. His investigations revealed that the most frequent pulmonary complication amongst mustard gas deaths was chronic bronchitis (81% of autopsied cadavers). Other pulmonary findings were progressive pulmonary fibrosis (9%), pulmonary infections and tuberculosis (29%), malignant cellular infiltration (4%) and aspergilloma (1%). As victims suffering from mustard-induced SPF could survive more than 10 or even 20 years instead of 3–5 years for IPF patients, it may be a reason for the authors to propose that ''pulmonary fibrosis is not compatible with survival of patients''. Current data from mustard victims suggest that the survival rate may not be comparable between IPF and mustard-induced SPF.
- The mean age reported for IPF patients was 63 years (Bjoraker et al., 1998), whereas it was 34.39 ± 5.95 years for patients exposed to mustard gas (Emad & Rezaian, 1997). Therefore, further epidemiological study may still

be needed to demonstrate whether mustard-induced SPF is compatible with the survival rate of patients.

- In the report by Emad & Rezaian (1999), the percent of diffusing capacity of carbon monoxide (DLCO) correlated well with the degree of pulmonary fibrosis, and the authors therefore proposed that ''the percentage of DLCO could be used as an objective monitor of the degree of fibrosis and also as a good predictor of prognosis in sulfur mustard gas-exposed patients with pulmonary fibrosis''.

Cytokines and pulmonary disorders

As it could be seen from Table 1, cytokines and chemokines have been well investigated in victims exposed to mustard by Emad, Ghanei and their colleagues from two different research groups in Iran (Aghanouri et al., 2004; Amiri et al., 2009; Attaran et al., 2010; Emad & Emad, 2007a,b,c,d,e; Ghazanfari et al., 2009; Pourfarzam et al., 2009; Yaraee et al., 2009; Zarin et al., 2010). However, results from Emad's group, and some of Ghanei's group (such as Aghanouri et al., 2004; Attaran et al. 2010; Zarin et al., 2010) are more relevant to pulmonary diseases as they focused on localized tissue changes of cytokines and chemokines in bronchoalveolar lavage fluid or lung biopsies. To link changes of cytokines and chemokines at system level (in serum) to pulmonary diseases may be too speculative as it has been well known that mustard could also induce inflammatory (cytokine and chemokine) changes in other organs such as skin (Arroyo et al., 2000, 2003, 2004; Blaha et al., 2000a,b; Cowan et al., 2002; Kehe et al., 2009; Ricketts et al., 2000; Sabourin et al., 2002; Tanaka et al., 1997; Tsuruta et al., 1996; Wormser et al., 2005), eye (Ghasemi et al., 2012), liver (Anand et al., 2009).

Mustard –induced cell oxygen metabolism impairment

In Section 5.1 ''HD-induced acute damage'', p. 694 of our paper, mustard-induced intracellular oxidative stress has been mentioned as the following: ''- - - the pathogenesis of mustard toxicity might go through three steps: (i) mustard bond target cell surface receptor, (ii) it activated intracellular reactive oxygen species (ROS) and reactive nitrogen species (RNS) leading to peroxynitrite (ONOO−) production and (iii) the increased ONOO− level damaged organic molecules leading to poly(adenosine diphosphateribose) polymerase (PARP) activation'', which may result in rapid depletion of intracellular NAD+, inhibition of cellular energy metabolism, protease release and cell death.

- - -''From Bench to Bedside''- - -

As we have mentioned in Section 4 ''Experimental study of HD-induced respiratory diseases in the animal models'', pp. 693–694, current animal models of mustard-induced respiratory diseases are different and are not able to imitate the pathophysiological changes and clinical manifestations observed amongst sulfur mustard victims. Hence, there is still no ideal models for specific lung diseases (such as bronchiolitis obliterans or bronchitis) induced by sulfur mustard. Clinical data obtained from victims 10 years after HD exposure indicated that 10.65% of them suffered from asthma, 58.55%, 8.62%, 9.64% and 12.18% from chronic bronchitis, bronchiectasis, airway narrowing and pulmonary fibrosis, respectively (Emad & Rezaian, 1997). As clinical data are mainly gathered from the late pulmonary sequelae of HD gas inhalation ($\geq$10 years), there is still no data to show the correlations between progressive changes of specific molecules to clinical pathogenesis at chronic stages. In view of the paucity of clinical data at early phases of mustard exposure, it will be a challenge to conduct laboratory investigations to uncover the role of HD in the pathogenesis of specific lung diseases (such as Bronchiolitis obliterans or bronchitis). Henceforth, the authors chose not to speculate or emphasize on ''the correlation between molecular aspects of sulfur mustard injuries and clinical pathogenesis of sulfur mustard''. Based on current data from both animal experiment and clinical investigation, we believe that it is still too early to ''use a 'From Bench To Bedside' approach in considering the health effects induced by sulfur mustard exposure'', especially for chronic stages effect of mustard in man. This is due to the factor that animal models are still at an immature stage, and there are not much data to link acute phase changes with the progressive pathophysiological late changes in the respiratory system of casualties exposed to sulfur mustard. Further extensive studies in ideal animal models, including large animal models of sulfur mustard exposure will significantly improve our understanding of the mechanisms of sulfur mustard-induced pulmonary diseases. This will help us to ''use a 'From Bench to Bedside' approach'' to design therapeutic approaches to effectively mitigate HD-induced respiratory diseases.

The mechanisms of chronic pulmonary consequences of SM exposure

In Figure 1 from the letter, Saburi and Ghanel described the mechanisms of chronic pulmonary consequences of HD exposure based on their previous research on victims 15 years after exposure to HD (Ghabili et al., 2011; Ghanei & Harandi, 2007, 2011). However, data indicated from the authors' research are insufficient to draw this mechanistic figure. Without detailed figure legends to explain the integrated mechanism, Figure1 could not stand alone. So far, no data could show the progressively pathophysiological changes of respiratory system in victims exposed to HD from the authors' research. The clinical data from the authors' group were mainly from the late pulmonary sequelae of HD gas inhalation ($\geq$15 years), it remains unknown for what really happens for the interactions among functionally different molecules and the health effect caused by their interactions. It seems too speculative to draw Figure 1 to reluctantly link different events sequentially or parallel. Some information may also be misleading. For instance, how much evidence support that ''Insufficient Cell Anti-Oxidant storage'' is an immediate effect of ''Cell & Tissue injury with SM in Acute Phase'', and that subsequently, ''Insufficient Cell Anti-Oxidant storage'' could induce (1) ''Membrane potential imbalance'', (2) ''Inflammatory modulators release, (3) Apoptosis & Necrosis and (4) Gene mutation regulating dysfunction''? HD can have direct effects such as alkylation

Table 1. Cytokines and chemokines in pulmonary disorders after sulfur mustard exposure.

Pulmonary disease including signs and symptoms	Sample size	Mean age (years)	Duration of disease (years)	Changes of cytokine or chemokine	Correlation with pulmonary disease	Reference
Secondary pulmonary fibrosis (SPF)	51 (18 HD-induced PF, 15 IPF, 18 Controls	Patients: 36.94 ± 4.54 Controls: 37.28 ± 4.26	20	Increased BALF MCP-1, MIP-α and MIP-1β	MCP-1, MIP-α and MIP-1β are associated with PF	Emad & Emad (2007a)
	29 (15 exposed, 14 controls)	Patients: 37.26 ± 5.10 Controls: 35.21 ± 4.64		Increased BALF IL-5, RANTES (CCL5) and eotaxin (CCL11)	IL-5, CCL5 and CCL11 contribute to eosinophil recruitment	Emad & Emad (2007b)
	36 (18 HD-induced PF, 18 controls)	Patients: 36.77 ± 4.63 Controls: 35.88 ± 4.67		Increased BALF IL-8 G-CSF GM-CSF	IL-8 G-CSF GM-CSF are associated with PF	Emad & Emad (2007c)
	38 (19 HD-induced PF, 19 controls	Patients: 36.83 ± 4.61 Controls: 36.00 ± 4.57		Increased BALF IL-8, IL-1β, IL-6, TNF-α, IL-12, EGF, IGF-1, TGF-β	IL-8 and TGF-β are associated with the degree of fibrosis	Emad & Emad (2007d)
Bronchiectas	54 (29 bronchiectasis, 25 controls)	Patients: 37.37 ± 4.56 Controls: 36.24 ± 4.75		Increased BALF IL-8, IL-1β, IL-6, TNF-α, IL-12	IL-8, IL-1β, IL-6, TNF-α, IL-12 are associated bronchiectas	Emad & Emad (2007e)
Chronic cough, Sputum Hemoptysis	494 (368 exposed, 126 controls)	SICS 372 exposed:	20	Serum TNF↓, IL-1α↓, IL-1β↓, IL-1Ra↓	Not clear	Yaraee et al. (2009)
Dyspnea Chest pain (Sardasht-Iran Cohort Study) (SICS)	500 (372 exposed, 128 controls)	Non-hospitalized (203): 43.4 ± 10.8 hospitalized (169): 44.4 ± 10.7 128 Controls		Serum MCP-1/CCL2↑, RANTES/CCL5↓, IL-8/CXCL8↓ Fractalkine/ CX3CL1↑		Ghazanfari et al. (2009)
	494 (369 exposed, 125 controls)	41.7 ± 9.8		Serum GM-CSF: no change		Amiri et al. (2009)
	468 (348 exposed, 120 controls)			Serum IL-6↓, IL-8↓		Pourfarzam et al. (2009)
COPD	80 (50 exposed, 30 controls)	Patients 46.3 ± 9.18 Controls: 47.8 ± 7.9	17.00 ± 6.00	Serum IL-6↑	Negatively correlated with airflow limitation	Attaran et al. (2010)
PF	235 (126 exposed, 64 not exposed, 33 normal control 12 IPF	Exposed: 41.5 ± 5.6 Not exposed: 42.25 ± 6.3 Normal control: 32- 40 IPF: 53-63	15	Increased BALF TGF- β1	Positively correlated to SPF, not IPF	Aghanouri et al. (2004)
Bronchiolitis obliterans (BO)	34 (20 exposed, 14 normal control	Patients: 38-56 Control: 43-64	15-16	Increased TGF-β1 TGF-β3 in lung biopsies	Positively correlated lung protection	Zarin et al. (2010)

BALF: Bronchoalveolar lavage fluid; COPD: Chronic obstructive pulmonary disease; EGF: epidermal growth factor; G-CSF: Granulocyte-colony stimulating factor; GM-CSF: Granulocyte-macrophage colony stimulating factor; IGF-1: insulin-like growth factor-1; IPF: Idiopathic pulmonary fibrosis; SICS: Sardasht-Iran Cohort Study; SPF: Secondary Pulmonary fibrosis; TGF-β: growth factors transforming growth factor-beta; TNF-α: tumor necrosis factor-alpha.

of DNA, proteins and membrane components as well as activation of inflammatory cells. TGF-β is a multifunctional cytokine which has a wide range of anti-inflammatory and profibroitic effect. It is produced by efferocytotic macrophages, suppresses the inflammation and enhances the regeneration of tissue. Previous study from the authors' group suggested that ''TGF-β1 and TGF-β3, but not TGF-beta2, secretion was a result of efficient efferocytosis in chemically injured patients, playing a protective role by improving airway remodeling and lung homeostasis in this group. These properties of TGF-β are consistent with long-time survival of chemical-injured people suffering from bronchiolitis obliterans'' (Zarin et al., 2010). However, in Figure 1, it is indicated that TGF-β1 might activate inflammatory cells leading to ''Cell & Tissue REPAIRE'' (is it a ''repair'' instead of ''REPAIRE''?). It is also confusing to mention two similar events, i.e. ''Inflammatory modulators release'' and ''Inflammatory cell activation'' for regulation of ''Cell & Tissue REPAIRE''. According to our knowledge, so far there is no publication to support that HD-induced gene mutation may result in defect in adherin and laminin, leading to subsequent defect in epithelialization. The authors may refer to the publications by Kehe et al. (2008) and Smith (2009), Figures 3 and 1 in the two papers, respectively, may be more informative and precise.

Genomic approach and others

In previous study of genomic DNA, the distinctive double mutations (G:C to A:T transition) were observed in two cases of lung cancers from Japanese HD factory workers, suggesting the correlation of HD exposure and DNA mutation (Takeshima et al., 1994). Hosseini-khalili et al. (2009) recently suggested that a single HD exposure may increase the risk of lung cancer development. Combined with many other reports mentioned in our publication (Tang & Loke, 2012), a comprehensive genomic study will certainly reveal more mutated gene and provide evidence for better understanding of the mechanism of HD-induced respiratory diseases.

We agree with Saburi & Ghanei (2013) that focusing on searching a possible commeasure point between antioxidant system and inflammatory pathway in future studies may provide a new therapeutic target for effective treatment of HD-induced human diseases. This investigation may however take some time to come into fruition.

Declaration of interest

This reply to the letter of Saburi & Ghanei (2013) was prepared by the authors during the normal course of their employment. Their employment affiliation is as shown on the cover page.

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