# Lung Carcinogenicity of Sulfur Mustard

**Article** *in* Clinical Lung Cancer · January 2010

DOI: 10.3816/CLC.2010.n.002 · Source: PubMed



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# Lung Carcinogenicity of Sulfur Mustard

Mostafa Ghanei, Ali Amini Harandi

## Abstract

Sulfur mustard (SM), a major potent chemical warfare agent, has been used for its acute toxic effects. Over time, unfortunately, many different long-term health effects of exposure to SM have been detected in humans. There are many available data from soldiers or civilians exposed to SM: testing programs, contaminated workers in factories who were involved with the production of SM, and animal and molecular studies. Today it seems that our data are enough to discuss the carcinogenic effects of exposure to SM—as an alkylating agent—many years after exposure. Herein, we review all available published documents regarding the lung carcinogenicity of SM after both long-term and especially short-term exposure in humans. In summary, it is well documented that SM can cause human lung cancer after long-term exposure, but there has not been strong and definitive evidence for only short-term and acute, single, high-dose exposure until now.

*Clinical Lung Cancer*, Vol. 11, No. 1, 13-17, 2010; DOI: 10.3816/CLC.2010.n.002
**Keywords:** Alkylating agent, Chemical weaponry, Chronic obstructive pulmonary disease, Mustard lung, p53

## Introduction

Sulfur mustard (SM; bis [2-chloroethyl] sulfide), also known as mustard gas, is the principal vesicant (blister inducer) and DNA alkylating agent that is extremely cytotoxic even at low doses.[1] SM was one of the major potent chemical warfare agents developed and used during World War I. Large stockpiles are still present in several countries.[2] It was used in Battle of Ypres in 1915 during World War I for the first time and then in 1917 against French troops in World War I as chemical warfare.[3] World War II has been called "the unfought chemical war" because millions of tons of chemical weapons had been produced but were never used. More recent use of SM has included the conflict between Egypt and Yemen from 1963-1967[4] and by Iraq against Iran in the Iraq-Iran war from 1984 to 1988.[5] There is also some concern that US military personnel who served in the Persian Gulf in 1991 during Operation Desert Storm might have also been exposed to SM.[6] Because of its status as a warfare agent, SM has not been widely evaluated in standard laboratory biologic testing systems. The record of human cancer induction after exposure to SM is based on data sets describing the response of soldiers in battles or in voluntary participation in testing programs, people who were involved with the production of SM and were thus exposed to toxic concentrations, and civilian victims in wartime conditions. The findings in humans have been further tested with studies in laboratory animals.

Sufficient data exist to recognize SM as a carcinogen after prolonged exposure.[7] Today it seems that our data are enough to discuss the carcinogenic effects of a single exposure to SM in humans many years after single high-dose exposure. Herein, we review and discuss all available documents from different languages regarding the carcinogenicity of mustard lung (ie, lung disorders after exposure to mustard gas) after both chronic and especially short-term but significant exposure in humans.

## Single High-Dose Exposure

The concentration of mustard in sufficiently high levels to induce signs of acute toxic response shortly after chemical exposure (ie, skin blistering) has been mostly considered as acute high-dose exposure.[8] Soldiers and civil populations once exposed to single high doses of SM are the main source of studies in this field. Because the various studies reported lung cancer in patients with long durations of exposure to SM, concern has been raised about single short-term exposure. In the case of World War I, there is evidence of a positive association, but with a low risk, between mustard exposure and increased risk of developing lung cancer up to 40 years after exposure.[7-11]

In a well-designed study, American soldiers with mustard-agent exposure were compared with soldiers who had pneumonia during the influenza outbreak of 1918 without a mustard exposure history, and with wounded soldiers. The frequency of respiratory cancers in the mustard-exposed group was somewhat higher in than the other

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Submitted: Aug 29, 2009; Revised: Oct 18, 2009; Accepted: Oct 27, 2009

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2 groups (ratio of observed to expected cases: SM, 1.47; pneumonia, 0.81; wounded, 1.15).[10] An additional study of this group of American soldiers with an additional 10 years of follow-up provided the same results. Deaths from respiratory cancer occurred in 2.5% of those exposed to SM, 1.8% of those who had had pneumonia, and 1.9% of a control group.[11] The risk of death from lung cancer among exposed subjects compared with controls was estimated at 1.3 (95% CI, 0.9-1.9), which in contrast to the findings of Case and Lea[9] did not suggest a strong carcinogenic effect. Case and Lea studied 1267 men in England and Wales from the 1914-1918 war. It showed that deaths from cancer of the lung and pleura occurred at twice the rate for the general population (standardized mortality ratio [SMR], 2; $P < .01$). It compared with controls and also had shown excessive deaths from bronchitis (SMR, 10; $P < .001$) as compared with nonexposed soldiers. Veterans who did have bronchitis without exposure to SM also had excess mortality because of lung cancer (SMR, 2; $P < .01$) as compared with controls. The authors suggest that the finding of a high incidence of lung cancer in both groups of veterans who had bronchitis does not support the action of SM as a direct carcinogen. It has been concluded that lung tissue damaged by either chronic bronchitis (or the etiologic agent that generated chronic bronchitis) or battlefield mustard agent exposures was more likely to become malignant than nondamaged tissue. They also supposed that it was possible that the dose of SM was not high enough to be carcinogenic and had not had a synergic effect. It should be considered that the underlying etiology that led to chronic bronchitis (eg, smoking or SM exposure) per se could be carcinogenic. Hence, pure tissue damage without carcinogenic risk factors, such as congenital cystic fibrosis, cannot cause lung cancer.

The effect of tobacco use was examined by Norman among a limited subgroup of veterans for which smoking histories were available.[11] The relative risk (RR) of lung cancer mortality among cigarette smokers who were exposed to mustard agents was approximately equal to that of the population of gassed veterans who stated that they did not smoke (RR, 4.3 vs. 4.4). Norman concluded that there was no evidence that mustard exposure and cigarette smoking "acting together produced either a smaller or larger relative risk of death from lung cancer than the sum of their separate effects." Thus, it was suggested that there was no substantiation for a synergistic effect between cigarette smoking and mustard exposure.[8,11] But in a recent immunologic study on high-dose-exposed soldiers to SM, preliminary data trends suggest an additive contribution of SM exposure and smoking to p53 immunoreactivity.[12]

The Chemical Warfare Service (CWS) carried out different types of experiments involved 60,000 human subjects. Chamber tests of various types were conducted to test the effectiveness of protective clothing and gas masks; however, SM could penetrate into the protective items.[13] More recently, a retrospective 50-year-mortality follow-up study was conducted by Bullman and Kang comparing the mortality of 1545 World War II US Navy veterans who received low-level nonlethal exposures of SM when voluntarily participating in mustard gas chamber tests between 1944 and 1945 to the mortality of 2663 nonexposed Navy veterans who served at the same location and time as a control group.[14] These veterans were exposed to SM while wearing protective clothing and masks and voluntarily participated in SM chamber tests. The levels of SM exposures experienced by World War II veterans were sufficient to cause skin reactions (erythema, vesicles, and ulceration). The mortality rate ratios for all cancer types among the total exposure group and all subgroups were less than 1. The authors indicated that this value was not statistically significant and that there was no excess of any cause-specific mortality associated with SM exposure among veterans. The authors noted that reliance on death certificates for cause of death and lack of data on potential confounders (smoking, drinking habits, and occupational history/exposure to carcinogens) were potential study weaknesses. Although the doses to participants were considered to be low-level by investigators, skin blistering showed that it was high enough to induce skin reaction.

During the Iraq-Iran war of the 1980s, SM was used extensively by Iraq against Iranian military and civilian populations.[5] This has served as a unique resource for recent researchers in this field for 2 decades. The case provides large-scale epidemic, clinical, and biomolecular studies on SM effects in humans. In the following, we summarize published documents on the carcinogenic qualities of SM that have been derived from studies on Iraq-Iran war victims.

A follow-up clinical study in 1996 on 197 Iraq-Iran war veterans with a single heavy exposure to SM gas and 86 nonexposed veterans as their control group found no bronchial carcinoma or other lung malignancies 10 years after exposure.[15]

In a cross-sectional study, 98 patients with protracted hemoptysis in association with history of a single exposure to SM were evaluated. No finding had been detected supporting malignancy in any cases via imaging and pathologic evaluations. Cytologic investigation of bronchial lavage for malignancy in all cases was negative. Pathology findings of specimens were 9% normal, 83% chronic inflammation, and 8% squamous metaplasia. It has been concluded that hemoptysis per se in acutely exposed SM patients could not be considered valuable evidence of lung malignancy, and it is more likely due to other pathologies of the respiratory system in patients exposed to SM. Nevertheless, close monitoring of these patients for early detection of any kind of malignancy was suggested.[16]

In a historical cohort study, 500 male veterans with a single high-dose exposure during the Iraq-Iran war were compared with veterans without exposure with the same demographic characteristics about 18 years after exposure. Only 3 cases of cancer (2 lung cancer and 1 lymphoma) were detected in the exposure group. The RR of cancer was 4.02 (95% CI, 0.45-36.1), and there was no statistically significant difference between the incidence of cancer in exposed and nonexposed groups.[17] In another cohort study, 500 individuals, including 372 from a civilian population from Sardasht, Iran, who had SM exposure in June 1987, were evaluated. No case with lung cancer has been reported.[18] These individuals are still under follow-up.

### *Molecular Approach*

Ludlum et al in 1986 stated that alkylation in the O6 position of guanine cannot be repaired by the enzyme O6-alkylguanine-DNA-alkyltransferase; therefore, despite their relatively rare occurrence (0.1% of mutations compared with 67% for N7 position in guanine) should be considered a causative mechanism for carcinogenicity after exposure to SM.[19] This finding has never been questioned by recent publications.

The failure of DNA repair after exposure to SM might result in programmed cell death via apoptosis.[20-22] First, the induction of

apoptosis after high-dose SM exposure, although responsible for many of the acute toxic effects, might also help to eliminate DNA-compromised cells and, second, the disturbance of DNA repair is reversible after a single exposure as well. Taken together these 2 processes might reduce the risk of cancer development because of single exposure to SM.

There are more molecular advantages for both diagnosis and treatment of gassed victims in some recent studies in Iran. The SM exposure might cause the development of susceptibility to mutations in tumor suppressor and oncogenes, such as p53 or *KRAS*. And p53, a critical tumor-suppressor protein, is an ideal focus of research because it accumulates within cells because of inhibited degradation after stress. Normally, the production of the protein initiates a cascade of events that results in cell cycle arrest and apoptosis, thereby preventing the survival and proliferation of genetically damaged cells.[23] However, the lung cells that lack a normal p53 protein are genetically unstable and thus more prone to carcinogenesis.[24,25] The mechanism of SM-induced carcinogenesis begins with cyclization of SM in the aqueous environment of a victim, to a highly reactive episulfonium ion that might alkylate DNA. If these are not repaired, these lesions can lead to nucleotide substitutions, most commonly the G-to-A transition.[26]

In a study on tumor suppressors, demographic information and tumor specimens were collected from 20 Iranian male patients with lung cancer with a history of single high-dose SM exposures during the Iraq-Iran war. Tissue samples were analyzed to identify mutations in the p53 and *KRAS* genes associated with SM exposure. A relatively early age of lung cancer onset (ranging from 28 years to 73 years with a mean of 48 years) in SM victims—particularly those in the nonsmoking population (mean age of 40.7 years)—was considered an indication of a unique etiology for these cancers. Seven of the 20 patients developed lung cancer before the age of 40. Five of 16 cancers from which DNA sequence data were obtainable provided information on 8 p53 mutations (within exons 5-8). These mutations were predominately G-to-A transitions, the most common mutation consistent with the DNA lesion caused by SM. Additionally, the presence of double- and triple-point mutations in the p53 gene was noted in the subjects; 2 of the lung cancers had multiple p53 point mutations, similar to results obtained from plant workers chronically exposed to a mustard agent. No mutations were detected in the *KRAS* gene. The distinguishing characteristics of lung carcinogenesis in this study suggest that a single exposure might increase the risk of lung cancer development in some individuals. What is noteworthy is that this is a pure molecular conclusion that specific mutations are related to specific cancers.[27] Nevertheless, no evidence has supported a direct causal relationship between single-dose mustard exposure and lung cancer in clinical and epidemiologic studies with large samples.

Takeshima et al studied p53 in a small Japanese population chronically exposed to SM through work at a factory producing mustard agent (factory workers).[23] The p53 analysis performed on 12 tumors isolated from Japanese plant workers showed 6 out of 12 lung tumors had at least 1 mutation in p53 (within exons 5-8), and 2 of the 12 tumor samples had double G-to-A transitions. It was concluded that these unusual double mutations might be characteristic of lung tumors caused by the interaction of SM with DNA and potentially reflects the high mutagenic capacity of mustard agent. Over 2000 p53 mutations have been reported in human lung cancers, and few double mutations have been documented thus far.[23,28,29] In a study of 15 patients exposed to an atomic bomb blast with lung adenocarcinoma or squamous cell carcinoma, 2 patients were found to have double mutations in p53.

In another study, the p53 immunoreactivity in bronchial epithelium of individuals with histories of tobacco use and/or SM exposure was evaluated, as a diagnostic marker to define late pulmonary complications of SM as mustard lung. In this study, 68 patients with chronic obstructive pulmonary disease (COPD) were segregated into 2 groups of 35 mustard-exposed patients (including 8 smokers) and 33 unexposed patients (including 16 smokers). Among nonsmokers, 41.2% of unexposed subjects and 14.8% of exposed subjects expressed p53. Among smokers, 25% of the unexposed group and 50% of the exposed group expressed the protein. Initial data trends suggest an additive contribution of SM exposure and smoking to p53 immunoreactivity. The first is the observation that, among nonsmoking participants, those with SM exposure exhibited lower p53 immunoreactivity than did those without previous SM contact. These results illustrate the use of p53 immunoreactivity in the characterization of COPD, including mustard lung.[12]

## Occupational Exposure

Definitive evidence of the carcinogenic action of mustard in humans comes from occupational exposures in poison gas plant workers in which they were exposed over a long time (ie, months and years). Occupational studies of Japanese, British, and German factory workers have shown elevated incidence of cancers of different organs, especially of the respiratory tract, among workers who manufactured SM agents. These results provide strong evidence for an association between mustard agent exposure and certain cancers due to high dose and long duration of exposure.

The Japanese Army operated a poison gas factory (1929-1945),[30-33] and Japanese workers experienced exposures to multiple poisonous agents, although mustard was produced in much larger quantities than the other agents. Some protective clothing was worn, but it was neither kept in good repair nor stocked in sufficient quantity. The duration of SM exposure in cases of lung cancer was 7-9 years, and the latent period for tumor induction was 17-20 years. Studies have shown definite increases in respiratory cancer among workers who produced mustard agent compared with office workers at the same factory.[7,31,32,34-38]

A study of British workers in a SM factory during World War II who had worked in the SM manufacturing process for 4-5 years showed that lung cancer deaths were also elevated in the occupational group when compared with the control, but the increase was not statistically significant. The authors suggest that differences in the cancer risk of the British and Japanese groups could have been because of better industrial hygiene practices in wartime England. In a cohort study of 502 workers involved in SM manufacturing between 1940 and 1945, a significant excess mortality was observed for carcinoma of the larynx and trachea (SMR, 7.5; $P < .02$).[39] In another study of 3354 British SM workers, significant excesses were observed compared with national death rates for deaths from

cancer of the larynx (SMR, 2.7; 11 deaths observed, 4.04 deaths expected; $P$ = .003), pharynx (SMR, 5.5; 15 observed, 2.73 expected; $P$ < .001), lung (SMR, 1.4; 200 observed, 138.39 expected; $P$ < .001), and upper respiratory sites combined.[40]

In another cohort, 245 German factory workers with previous occupational exposure to SM have been monitored for over 20 years. There was a statistically significant increase in malignant tumors, especially bronchial carcinoma, bladder carcinoma, and leukemia.[41] Other epidemiologic studies of German poison gas factory workers without adequate protection have also indicated increased occurrence of respiratory cancers.[42]

## Animal Cancer Studies

Animal studies showed tumors after inhalation exposure to SM.[7] A series of experiments have indicated that mustard is genotoxic, producing chromosome and gene mutations in vitro in a dose-related fashion.[43] Excepting several studies by the injection method, we only focused on experiments conducted in which subjects were exposed to SM by inhalation. Heston and Levillain in 1953 exposed 80 mice once for 15 minutes to very high levels, but an unknown vapor concentration, of SM. Surviving and control mice were followed for 11 months. Finally, 33 of 67 experimental mice developed pulmonary tumors, compared with 21 of 77 control mice.[44] In several studies, McNamara et al exposed animals to SM continuously or intermittently for periods from 1 to 52 weeks. The results demonstrated that SM readily produced skin malignancy in rats, but no excess tumors at other sites, and in control mice for similar period. Further, at similar inhalation exposure but inadequate follow-up time, no increase in agent-related skin or other malignancies in experiments with dogs, guinea pigs, rabbits, and strain A/J mice have been observed.[45] The significance of this finding for humans is difficult to determine because of their specific genetic tendency to develop lung tumors. Strain A mice have extremely high genetic susceptibility for the development of pulmonary tumors. Also, testing of an extremely high dose of the exposure concentration was considered as study weakness to estimate cancer potency.[46] However, this finding could provide for better understanding of the molecular mechanism contributing to the pathogenesis but not the incidence of cancer.

## Discussion

There are some limitations in most studies in this field. Usually only healthy individuals are allowed into the military, and their health is monitored while they are in the military; therefore, this group is healthier than the general population. This effect might continue even after individuals leave active duty. However, few studies on different target population (eg, on civil Iranian populations or comparing veterans without exposure) did not show different results. Because smoking is common for military personnel,[47] it is the main confounding factor that can play an important role in obtained results. Unfortunately, most studies in this field failed to exclude smoking as the main confounding factor. Few well-controlled studies strongly suggested additive contribution of SM exposure and smoking to cause cancer.

Although there are some molecular and immunoreactivity clues for the carcinogenicity of mustard gas after a single high-dose exposure, other epidemiologic studies on large scales have not shown significant elevated risk for carcinogenicity.

Moreover, the response of subjects after exposure to SM is supposed to be case dependent; various internal factors (ie, healthy status, underlying disease, and genetic tendency) and external factors (ie, toxicities, duration and frequency of exposure, coexposure, emergent and follow-up medical care, smoking, and synergistic effect of occupational exposure) differ from one person to another.

While it is well documented that prolonged exposure to SM even at low doses was associated with an increased risk of lung or other respiratory tract cancers, so far there is no such strong and sufficient evidence for just short-term and one-time, acute, single high-dose exposure. It could not be concluded whether a small number of reported lung cancers after single high-dose exposure are due to direct induction of SM or whether they are caused by confounding factors such as smoking, which is considered a definite carcinogen.

## Disclosures

The authors report no relevant financial conflicts of interest.

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