Biological monitoring of the ethylene oxide gas effects on medical utilities sterilization exposed staff

Mahmoud M. Kamel\textsuperscript{a}, Mahmoud A. I. Hewehy\textsuperscript{b}, Ahmed H. M. Hussein\textsuperscript{c}, Waleed Samyd,\textsuperscript{*}

\textsuperscript{a}National Cancer Institute, Cairo University.
\textsuperscript{b}Basic Science Department, Institute of Environmental Studies and Research, Ain Shams University.
\textsuperscript{c}VACSERA.
\textsuperscript{d}Departments of Internal Medicine, Faculty of Medicine, Tanta University Egypt & Taif College Of Medicine, KSA.

Abstract. Chronic exposure to Ethylene Oxide (EtO) gas was suggested to be associated with many health hazards. This study was conducted on thirty one workers exposed to EtO gas in different production areas and classified into three groups; group I included seven workers with direct exposure, group II included thirteen workers with partial exposure and group III included eleven workers with indirect exposure. One group included 20 non exposed persons and served as a control group (group IV). All of them underwent analysis of complete blood count, T-lymphocytes subsets (CD3, CD4, CD8) by flowcytometry technique, serum IgG concentration by ELISA technique and p53 gene mutational changes. Platelet count was significantly reduced in all exposed groups. Both CD3\% and CD4\% were significantly decreased in group I and II ($p \leq 0.05$, $p \leq 0.001$) respectively. Also, the absolute value of T-helper lymphocytes was significantly reduced in group I and II ($p \leq 0.05$). However, CD8\% was significantly increased only in group III ($p \leq 0.05$). A significant elevated value of total IgG was found in group I and II ($p \leq 0.05$). Variable gene mutation was detected in p53 exons (5b, 6 and 7) which were 28.5\% (group I), 7.7\% (group II) and 9\% (group III) for exon 5b, 28.5\% (group I) and 15.4\% (group II) for exon 6 and 14.2\% (group I), 7.7\% (group II) and 9\% (group III) for exon -7. There was significant reduced platelet count in all exposed groups. Both CD3\% and CD4\% and the absolute value of T-helper lymphocytes were significantly reduced in group I and II. EtO gas exposed personals showed a remarked IgG concentrations increments. There were genetically observed mutational changes located at p53 gene post EtO gas exposure.

Key words: Ethylene oxide gas chronic exposure, T-lymphocytes subsets (CD3, CD4, CD8), p53 gene mutation

1. Introduction

Ethylene Oxide (EtO) gas is an important industrial chemical with widespread uses directly in the gaseous form for the fumigation and sterilization of a variety of heat sensitive materials such as agricultural, medical and hospital equipments (1). The EtO-gas sterilizes products by means of an alklyation’s reaction that destroys an organism’s ability to reproduce.

*Correspondence: Waleed Samy
Departments of Internal Medicine, Faculty of Medicine, Tanta University Egypt
E-mail: wsmohamed1@yahoo.com
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Products must be placed in breathable packaging that allows the gas to penetrate the sterile barrier and reach all surfaces of the device (2). The uptake of EtO occurs mainly through inhalation and is critically dependent on the alveolar ventilation rate (3). Dermal absorption is unclear (4). The use of EtO gas necessitates strict precautions as it is considered to be a human carcinogen capable of increasing the incidence of leukemia and/or lymphoma (4,5) Besides its carcinogenic properties, EtO gas is irritant (6) and may induce abortion (7). In order to prevent exposure hazards, potential workplaces must be aerated and the gas must be monitored cautiously while in use (8). So, The Occupational Safety and Health Administration (OSHA) and the National Institute for Occupational Safety and Health
(NIOSH) recommended several approaches for monitoring workers exposed to EtO gas as end determination of blood ethylene glycol level, (9) hemoglobin adducts (10, 11) and glutathione derivatives, such as thioethers metabolites (12) or HEMA in urine (13). However, for some of these biomarkers, genetic polymorphisms of the enzymes metabolizing EtO may occur (14).

Therefore, the present work aimed to investigate the potential changes in EtO gas exposed personnel in one of the medical equipment producing company in Egypt concerning hematological, immunological and genetic parameters.

2. Materials and methods

This cross-sectional study was conducted on thirty one male workers exposed to EtO gas at one of the factories which uses this gas for sterilization of medical products. All these workers wear protective equipments like special gowning masks and gloves. Also, the work was carried out according to hygienic programs of the occupational safety measures used in this factory. All workers completed a socio-medical questionnaire which included age, job description, type of exposure, working hours, working years, smoking habits, family and past history of diseases such as asthma, allergy, immunization, exposure to X-ray, repeated infections, medication and history of malignancy.

There were four groups in the study; the first three groups were classified according to their contact level with EtO gas, one group served as control:

- Group I: Seven workers in direct contact sites (the sterilization and aeration chamber).
- Group II: Thirteen workers in partial contact sites (the visual inspection of final products department).
- Group III: Eleven workers in indirect contact sites (the assembly and injection department).
- Group IV: Twenty healthy male of matched ages (31.13±7.22) served as control. They were non-EtO gas exposed personnel working in other factories in the same area. Smokers were excluded from the study.

2.1. Air monitoring

Evaluation of the EtO gas level was done by air samples from three different working areas in the factory (sterilization and aeration room, final inspection room and assembly and injection room) and a 4th area which is a non-EtO exposed site by the use of Meran A1B2 device (Scietech-USA) to estimate the concentration of EtO gas traces and expressed as units in part per million (ppm) (15). The Egyptian environmental law endorses that it should not exceed 10 ppm and according to the International Environmental Regulations it should not exceed 5 ppm (16, 17).

2.2. Methods

Blood samples that were collected from the workers during our visit to three working sites in the factory and from the control group were used for the following tests:

- a. Complete Blood Count (CBC) on cell counter auto-analyzer.

Table 1. Primary sequences for p53 tumor suppressor gene (exons from 5a to 8).

<table>
<thead>
<tr>
<th>Exon NO.</th>
<th>Sequences</th>
<th>Size (base pair)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exon - 5a</td>
<td>F: 5’- CCA GTT GCT TTA TCT GTT CA - 3’&lt;br&gt;R: 5’- TGT GGA ATC AAC CCA CAG – 3’</td>
<td>139 kilo Daltons</td>
</tr>
<tr>
<td>Exon - 5b</td>
<td>F: 5’-CAA CTG GCC AAG ACC TGC – 3’&lt;br&gt;R: 5’- AAC CAG CCC TGT CGT CTC T – 3</td>
<td>191 kilo Daltons</td>
</tr>
<tr>
<td>Exon - 6</td>
<td>F: 5’-CTC TGA TTC TCT ACT GAT TGC – 3’&lt;br&gt;R: 5’- GAG ACC CCA GTT GCA–AACCA-3’</td>
<td>163 kilo Daltons</td>
</tr>
<tr>
<td>Exon - 7</td>
<td>F: 5’-TTG CCA CAG GTC TCC CCA A – 3’&lt;br&gt;R: 5’- AGG GTG GCA AGT GGC TCC – 3’</td>
<td>190 kilo Daltons</td>
</tr>
<tr>
<td>Exon - 8</td>
<td>F: 5’- CCT TAC TGC CTC TTG CTT C – 3’&lt;br&gt;R: 5’- CGC TTC TTG TCC TGC TTG C – 3’</td>
<td>199 kilo Daltons</td>
</tr>
</tbody>
</table>
c. Immunophenotyping analysis was performed on the mononuclear cells from fresh blood samples. It was performed with FACS vantage-SE immunocytometry systems (Becton Dickinson -USA) by the use of specific monoclonal antibodies for assessment of T-cell lymphocytes (CD3, CD4 and CD8) (Dako-USA).

Detection of P53 gene mutation by PCR.

<table>
<thead>
<tr>
<th>Area</th>
<th>Area class</th>
<th>No. of air samples</th>
<th>EtO gas levels (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blank (other factories)</td>
<td>Non-exposed</td>
<td>20</td>
<td>ND*</td>
</tr>
<tr>
<td>Sterilization and aeration room</td>
<td>Direct</td>
<td>20</td>
<td>4.20 - 7.10</td>
</tr>
<tr>
<td>Final inspection room</td>
<td>Partial</td>
<td>20</td>
<td>0.70 - 2.50</td>
</tr>
<tr>
<td>Assembly and injection room</td>
<td>Indirect</td>
<td>20</td>
<td>0.05 - 0.041</td>
</tr>
</tbody>
</table>

*ND; Not Detected.

2.3. Evaluation of p53 gene exons mutations
Comparing the resulted scanned bands with certain standard known bands submitted with the primers sequences for p53 tumor suppressor gene, the evaluation was available to judge on the exons (5a - 5b - 6 - 7- 8) if there were possibilities for mutations occurrence.

2.4. Statistical methods
Data was analyzed using (SPSS-win) statistical package version-15. Numerical data were expressed as mean ± standard deviation (SD), median and range. Qualitative data were expressed as frequency and percentage. For quantitative data, comparison between two groups was done using Mann-Whitney test for variables not normally distributed. Comparison between 3 groups was done using Kruskal-Wallis test (non-parametric ANOVA test) followed by post-Hoc "Schefe test", which is used to compare pairs of groups applied to the rank of variables. Relationship between different numerical variables was tested using Pearson’s correlation. Correlation coefficient (r) of 0.5 was considered fair correlation, if more than 0.5 and less than 0.75, it was considered good correlation, and if > 0.75, then it was considered as very good correlation. A stepwise multiple regression analysis was done to find the independent variables associated with EtO effects. Results were considered significant at p<0.05.

3. Results
The mean age of the workers groups was 33.23±6.13 and the working years ranged from 1 to 23 years.

3.1. Assessment of the residual EtO gas air content
Residual EtO gas remained after sterilization chamber offloading and spread due to the air circulation was determined in different production areas. The mean concentrations of EtO (ppm) detected in different areas were presented in table 2.

3.2. Hematological changes
The mean Hb concentration and T-lymphocytes count (TLC) in all EtO exposed groups showed non significant changes compared to the control group. However, platelet count significantly decreased in groups I and II compared to the control group (table 3).

3.3. The immunological changes
The immune reactivity of EtO exposed personnel was monitored based on the determination of changes in T-lymphocytes subsets. There was a highly significant reduction in the mean CD4% and CD3% of both group I and II (p<0.001 and p<0.05, respectively) compared to the control group.
Table 3. Evaluation of the mean hematological parameters post ethylene oxide exposure

<table>
<thead>
<tr>
<th>Groups</th>
<th>Hb (g/dl) M±SD</th>
<th>p</th>
<th>PLT (x10^3/cmm) M±SD</th>
<th>p</th>
<th>TLC (cells/mm³) M±SD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>14.36 ±0.98</td>
<td>&gt;0.05</td>
<td>209.14 ± 47.78</td>
<td>≤0.001</td>
<td>7860 ± 2440</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Group II</td>
<td>14.37 ±1.35</td>
<td>&gt;0.05</td>
<td>256.31 ± 69.56</td>
<td>≤0.05</td>
<td>7600 ± 1380</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Group III</td>
<td>14.75 ±0.82</td>
<td>&gt;0.05</td>
<td>215.36 ±72.58</td>
<td>≤0.05</td>
<td>6470 ± 1720</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Group IV</td>
<td>14.35 ±0.92</td>
<td></td>
<td>305.7 ± 49.63</td>
<td></td>
<td>7420 ± 1297</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Evaluation of the Clusters of differentiation T-lymphocyte subsets (%) changes post ethylene oxide gas exposure

<table>
<thead>
<tr>
<th>Groups</th>
<th>CD3 (%) M±SD</th>
<th>p</th>
<th>CD4 (%) M±SD</th>
<th>p</th>
<th>CD8 (%) M±SD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>37.29 ±17.83</td>
<td>≤0.05</td>
<td>23.71 ±12.32</td>
<td>≤0.001</td>
<td>13.57 ±8.54</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Group II</td>
<td>38.38 ±28.07</td>
<td>≤0.05</td>
<td>22.15 ±15.93</td>
<td>≤0.001</td>
<td>16.15 ±13.59</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Group III</td>
<td>69.73 ±12.07</td>
<td>&gt;0.05</td>
<td>39.45 ±9.11</td>
<td>&gt;0.05</td>
<td>30.27 ±7.80</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Group VI</td>
<td>60.85±12.36</td>
<td></td>
<td>45.35 ±14.55</td>
<td></td>
<td>20.65 ±4.46</td>
<td></td>
</tr>
</tbody>
</table>

Table 5. Evaluation of the Clusters of differentiation T-lymphocytes subsets absolute counts variations post EtO gas exposure

<table>
<thead>
<tr>
<th>Groups</th>
<th>Absolute CD3 count M±SD</th>
<th>p</th>
<th>Absolute CD4 count M±SD</th>
<th>p</th>
<th>Absolute CD8 count M±SD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>1494.14 ± 873.21</td>
<td>&gt;0.05</td>
<td>730.0±465.05</td>
<td>≤0.05</td>
<td>378.14±251.31</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Group II</td>
<td>1084±764.33</td>
<td>&gt;0.05</td>
<td>617.62±407.53</td>
<td>≤0.05</td>
<td>464.46±400.96</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Group III</td>
<td>1696.18±543.81</td>
<td>&gt;0.05</td>
<td>963.27±53.58</td>
<td>&gt;0.05</td>
<td>727.36±246.17</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Group IV</td>
<td>1573.95±495.1</td>
<td></td>
<td>1181.80±482.72</td>
<td></td>
<td>533.2±174.20</td>
<td></td>
</tr>
</tbody>
</table>

with non significant change in both CD4% and CD3% in the group III (p>0.05). On the other hand, the mean CD8% significant elevated only in group III (p<0.05), while rest of the exposed groups showed non-significant changes; (p>0.05) compared to the control group (table 4). Regarding the absolute value of T-lymphocytes subsets, only the absolute number of CD4 positive lymphocytes (T-helper cells) was significantly reduced in group I and II (p<0.05), while other parameters showed non-significant changes (table 5).

The mean values of IgG were significantly elevated in group I and II compared to the control group (p< 0.05). While, the mean total IgG in group III did not change significantly compared to that of the control group (p>0.05) (table 6).

3. 4. Genotoxicity of EtO gas exposure

EtO gas exposure showed a variable effect on the p53 gene exons depending on the type of exposure. Both exon-5a and exon-8 showed no mutational changes, while exon-5b showed mutational changes of about 28.5% in group I, 7.7% in group II and 9% in group III. Also, exon-6 showed mutational changes of 28.5% in group I and 15.4% in group II. Exon-7 showed mutational changes of 14.2%, 7.7 % and 9% for group I, group II and group III, respectively (table 7).
Correlation analysis done between the working years, age of the workers who was exposed to EtO gas and different hematological and immunological parameters revealed that the absolute number and the percent of T-helper cells (CD4) was the most affected parameter as it is decreased in relation to both age and working years of the studied population (fig 1-2). After stepwise regression analysis, it is found that EtO gas level in different production areas was the only independent predictor to the development of EtO effects.

### 4. Discussion

EtO is an important industrial chemical with widespread uses directly in the gaseous form. It is highly soluble in blood and quickly absorbed from respiratory passages and gastrointestinal tract (2). Concerning the EtO gas air content loaded in different production areas included in the present study, all measured residual EtO levels were in the normal levels according to the recommendations reported by different committees; the Egyptian Environmental Regulations (EER) and the International Environmental Regulations, as recorded by OSHA, 2004 (17). This was attributed to the hygienic program and aeration facilities applied in the producing plant of interest.

The biological drawbacks of EtO gas exposure as referred by the WHO and environmental pollution organizations including hematological, oncogenic and immunological ones relatively related to the type of exposure especially those work in medical devices sterilization. The recorded data of the present study was coincided with Marsh et al. (2006) (20) who recorded no hematological changes in 36 male workers exposed to EtO gas at 0.05 ppm (0.09 mg/m) level for eight hours on a TWA basis and in 84 male workers exposed to 1 ppm (1.83mg/m3) or less. Concerning hematological parameters it was noticed that PLT count was significantly decreased in both group I and II personnel. Data recorded was opposite to that of the WHO (1985) (21) which revealed some hematological changes of rats exposed to 173 mg/m3 of EtO gas such as induced leucocytes in both sexes, and a decreased red blood cell count accordingly hemoglobin level in females. Some of these rats had leukemia. Also, Schulte et al. (1995) (22) recorded a reduced hematocrit, in turn hemoglobin concentration was predominant in 59 females employed at hospitals in the United States and Mexico exposed to EtO gas leakage from sterilizers (an average, cumulative exposure

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### Table 6. The mean total IgG concentration (mg/dL) in sera of EtO gas exposed persons

<table>
<thead>
<tr>
<th>Groups</th>
<th>Total IgG conc. (mg/dl) M± SD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>1380.14 ± 352.43</td>
<td>p≤ 0.05</td>
</tr>
<tr>
<td>Group II</td>
<td>1479.62 ± 398.02</td>
<td>p≤ 0.05</td>
</tr>
<tr>
<td>Group III</td>
<td>1313.45 ± 406.27</td>
<td>p&gt; 0.05</td>
</tr>
<tr>
<td>Group IV</td>
<td>1102.60 ± 212.60</td>
<td></td>
</tr>
</tbody>
</table>

### Table 7. The spectrum of p53 gene mutations in ethylene oxide exposed staff relatively to exposure conditions

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total cases</td>
<td>+Ve No</td>
<td>+Ve (%)</td>
</tr>
<tr>
<td>Exon-5a</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Exon-5b</td>
<td>7</td>
<td>2</td>
<td>28.5</td>
</tr>
<tr>
<td>Exon-6</td>
<td>7</td>
<td>2</td>
<td>28.5</td>
</tr>
<tr>
<td>Exon-7</td>
<td>7</td>
<td>1</td>
<td>14.2</td>
</tr>
<tr>
<td>Exon-8</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
level for four months was 32 ppm for a hour or more).

Referring to the EtO gas immunotoxicity, the present study revealed that mean total IgG concentrations was significantly elevated in group I and II, while in group III there was a non-significant elevation compared to the control group. The data of the current study were in agreement with data presented by Warbrick et al. (2002) who found that chemicals could cause sensitization of the respiratory tract and occupational asthma, could affect the induction of IgG concentrations and it was time and dose dependent (18). In addition, Santoro et al. (2007) reported that patients receiving long-term hemodialysis using EtO gas sterilized disposable medical equipments, the detected total IgG concentrations were affected and some of them

Fig. 1. Correlation between working years (years) of study population exposed to ethylene oxide gas and absolute CD4 (cells/mm$^3$).

$*_{\text{cmm}}=\text{mm}^3$

Fig. 2. Correlation between age (years) of study population exposed to ethylene oxide gas and absolute CD4 (cells/mm$^3$).
had antibodies to EtO gas, especially those suffering allergic reactions had borderline elevated IgG concentration (23).

These results demonstrated a significant relationship between the presence of IgG level due to EtO exposure and hemodalysis-related allergic reaction in exposed patients. Also to assure the immunotoxicity due to EtO gas exposure, the flow cytometry (FC) technique was used in the present study, according to Luoping et al. (2008) to identify T- and B- cells subtypes post EtO-gas exposure (24). Both group I and II exposed personnel showed a significant decrease in CD3% and a highly significant decrease in CD4%. Only the group III personnel showed a significant increase in CD8%. These data was coincided with that of Tryphonas (2001) who studied the adverse effects of different environmental contaminants agents including EtO gas on several organs and tissues of the immune system in the exposed laboratory animals (25).

Evaluation of the potential risk of environmental contaminants exposure to the human immune system is currently accomplished via extrapolation of experimentally derived animal data to humans. Data indicated a compromised immune system functions in the exposed populations and significant functional effects on both humoral and cellular aspects of immunity as a general. The author’s data revealed that there were reductions on both CD3 and CD4.

Concerning exposure time it was reported that short term exposure (one month) to EtO gas in a plant during 1942 -1979 showed a significant negative correlations between exposure time and the T lymphocytes including total T lymphocytes, CD3 and T-helper cells according to Lars et al. (1988) (26). In the mean time long term exposure as recorded by Van Sittert et al. (1985); showed that the duration of employment in EtO gas manufacturing was negatively correlated with the percentage of T-lymphocytes (27). Tompa et al. (2006) mentioned that EtO gas exposure could alter the ratio of lymphocyte subpopulations and might cause changes in the activation of lymphocytes and thus specific immunological markers could be monitored to assess exposure (28). In stepwise regression analysis, it is found that EtO gas level in different production areas was the only independent predictor to the development of EtO effects.

Mouse models of cancer have provided some insight as illustrated by different studies carried out by Christopher et al. (2006) in which mutagenic reactivity was detected post EtO gas inhalation by mice and probably in man and that was attributed to its electrophilicity, it could alkylate cellular macromolecules as DNA and proteins (29). Also, EtO metabolites might induce mutagenicity leading to protein sequence shifting. Oncogenicity to human was proved too, that for the effects of EtO gas on basic genetic material within the cells of living mammals including man (30). It was important to understand exactly how dysfunctional p53 gene was contributed to the development of cancer. Remarkably, the definitive roles of p53 gene in the development of cancer were incompletely understood. Accordingly, p53 gene was considered to be monitored concerning the mutational points induced. p53 gene was found to be involved in oncogenesis of diverse types of cancer worldwide. p53 gene was mutated in at least 50% of human cancer, inducing most tumor types (31). Gen-Tannini et al. (1995) reported that p53 mutation was a precursor for cancer incidence (32). These p53 gene mutations were selected after tumor cell enrichment by cell sorting based on differences in DNA content using PCR and single-strand conformational polymorphism (SSCP) analysis in 24 surgical specimens' primary gastric cancer. p53 gene mutations were detected in the exons 4-8 resembled 64% (9 of 14 cases) of aneuploid tumors. Accordingly, genotoxicity of EtO gas exposure was considered in the present study and data revealed that variable mutational patterns were detected in humans exposed to EtO gas related to type of exposure, whereas both exon -5a and exon-8 showed the same integrated sequence pattern, while exon-5b, exon-6 and exon-7 showed mutational changes in exposed test groups. Coggon et al. (2004) reported that there were cancer incidence probabilities due to the mutational changes found in the p53 gene exons especially at (5b-6-7) (33). Environmental Protection Agency (EPA) found that EtO has the potential to cause adverse health effects to hospital and healthcare facility workers who are involved with the EtO sterilization process for long-term (greater than 6 months). Also, both long-term non-cancer and cancer risks are of concern (34). According to International Agency for Research on Cancer (IARC) EtO is carcinogenic to humans and defined as a Group 1 chemical according to IARC classification (35).

5. Conclusion

Monitoring of biological drawbacks of EtO gas exposure as illustrated in the present study showed that there was a significantly reduced platelet count in all exposed groups. Both CD3% and CD4% and the absolute value of T-helper lymphocytes were significantly reduced in group
I and II. EtO gas exposed personals showed a marked IgG concentration increments. There were increases in the immune system responses either on the level of the T-helper cells (decreased levels) or on the other side T-suppressive cells (increased levels). There were genetically observed mutational changes located at p53 gene post EtO gas exposure.

5.1. Recommendation

Workers exposed to EtO gas seem to be more labile to many hazards as increased liability to infection and may have a higher risk to develop many cancers due to detection of variable gene mutation on p53 exons. So these workers must have a pre-employment and regular follow up with continuous substitutions of personnel especially in the higher risk exposure areas concerning the exposure dose and duration to fulfill the substitution necessity to minimize these risks.

References


