Evidence-Based Practice Group
Answers to Clinical Questions

The Effects of Sb_2O_3 on Human Health

A Rapid Systematic Review

Prepared by	Dr. Craig Martin Manager Medical Services, Evidence-Based Practice Group
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WorkSafeBC

About this report

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About the Evidence-Based Practice Group

The Evidence-Based Practice Group was established to address the many medical and policy issues that WorkSafeBC officers deal with on a regular basis. Members apply established techniques of critical appraisal and evidence-based review of topics solicited from both WorkSafeBC staff and other interested parties such as surgeons, medical specialists, and rehabilitation providers.

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Contact information

Address	Evidence-Based Practice Group WorkSafeBC PO Box 5350 Stn Terminal Vancouver BC V6B 5L5
Email	craig.martin@worksafebc.com
Phone	604 279-7417
Toll-free	1 888 967-5377 ext 7417

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Background

- In their effort to evaluate selected chemicals from the 2021, 2022, 2023 and 2024 threshold limit value (TLV) – time-weighted average (TWA) document published by the American Conference of Governmental Industrial Hygienists (ACGIH), the WorkSafeBC Exposure Limit Review Committee (ELRC) tasked the Evidence-Based Practice Group (EBPG) to investigate the health effects, regarding to the development of lung cancer and/or other non-cancer lung diseases, of occupational exposure to antimony trioxide (Sb_2O_3) with a significant lowering of the TLV-TWA. In their 2021 publication, the ACGIH lowered the TLV –TWA of Sb_2O_3 to 0.02 mg/m^3 from a previous level of 0.5 mg/m3 in 1978/1979. In their documentation[1], the ACGIH stated that this lowering in the TLV – TWA of Sb_2O_3 was expected to protect against non-malignant and malignant lung effects.
- The EBPG began the investigation by exploring the chapter on Sb_2O_3 that is available in the ACGIH TLV/BEI (Biological Exposure Indices) Guidelines Documentation and Data[1]. In this documentation[1], the ACGIH stated that a TLV-TWA of 0.02 mg/m3 in inhalable particulate matter was recommended based on extrapolation to humans from the dose causing lung pathology in experimental animals in chronic inhalation studies; and was expected to protect against non-malignant and malignant lung effects. With regard to other human health effects, this document[1] identified Sb_2O_3 causing upper and lower respiratory tract irritation, cataracts, pneumonitis as well as pneumoconiosis. With this information, the EBPG set out to conduct a systematic review of the literature, with the objective of investigating whether occupational exposure to Sb_2O_3:
    - is, causally, associated with the development of lower respiratory tract irritation, changing in lung function, any other lung effect either malignant or non-malignant as well as cataract.
    - in the event that such a (causal) association exists, what level of occupational exposure was associated with the development of the disease of interest.

Methods

- A comprehensive and systematic literature search was conducted on February 11, 2025.
- The search was done on commercial medical literature databases as well as on non-commercial occupational health and safety database. The commercial medical literature databases, including BIOSIS Previews (1969 to 2008), Embase (1974 to 2025 Week 06), Medline and Epub Ahead of Print, Medline In-Process, In-Data-Review & Other Non-Indexed Citations, Medline Daily and Medline (1946 to February 10, 2025), Joanna Briggs Institute Evidence Based Practice Database (Current to January 29, 2024), Cochrane Clinical Answers (January 2025), was available through Ovid platform.
- NIOSHTIC-2, the non-commercial occupational health and safety database, was accessed its portal at https://www2a.cdc.gov/nioshtic-2/AdvSearch2.asp. Its houdl be noted that NIOSHTIC-2 is a searchable bibliographic database of occupational safety and health publications, supported in whole or in part by the US National Institute for Occupational Safety and Health (NIOSH).
- A combination of keywords was employed in these searches. On searching the commercial medical literature databases, these keywords were employed:

    1. (antimony trioxide) **OR** (1309-64-4) OR Sb_2O_3 **OR** (antimony iii oxide) **OR** (antimony sesquioxide) **OR** (antimonous oxide) **OR** (flowers of antimony) **OR** (oxo-oxostibanyloxystibane)
    2. pneumonitis
    3. pneumoconiosis
    4. (lower respiratory tract irritation)

5. (lung function)
6. (respiratory tract irritation)
7. (lung pathology) **OR** (lung effect*) **OR** (lung pathologies)
8. lung
9. (non-malignant chronic effect*)
10. (chronic effect*)
11. cataracts
12. (malignant chronic effect*) **OR** carcinogenicity **OR** carcinogen **OR** malignancy
13. #1 **AND** #2
14. #1 **AND** #3
15. #1 **AND** #4
16. #1 **AND** #5
17. #1 **AND** #6
18. #1 **AND** #7
19. #1 **AND** #8
20. #1 **AND** #9
21. #1 **AND** #10
22. #1 **AND** #11
23. #1 **AND** #12

A simplified and more general keywords were employed in searching NIOSHTIC-2 database. These keywords were:

24. (antimony trioxide)

- No limitation, such as on the language or date of publication was implemented in these searches.
- Manual searches, on the references of the articles that were retrieved in full, were also done.
- Additional search was also conducted on the websites of the International Antimony Association (i2a). i2a is an organization representing the producers, importers and users of multiple antimony substances and is based in Brussels (https://www.antimony.com/about-us/).

Results

- Search results:
    - No published studies were identified on pneumonitis (search #13), lower respiratory tract irritation (search #15), respiratory tract irritation (search #17), lung pathology (search #18), non-malignant chronic effect (search #20), (any) chronic effect (search #21) as well as the search on NIOSHTIC-2 database (search #24).
    - Seven[2-8], two[9-10], 31[11-41], one[42] and 20[43-62] published studies were identified from search #14 (on pneumoconiosis), search #16 (on lung function), search #19 (on lung), search #22 (on cataracts) and on search #23 (on malignancy), respectively. Upon examination of these titles and abstracts of the 61[2-62] published studies, 11[2,4,5,6,14,15,35,36,44,52,54] studies were thought to be relevant and were retrieved in full. However, we were not able to retrieve one[4] of these 11[2,4,5,6,14,15,35,36,44,52,54] studies. In this paper[4], Li et al reported an analysis of lung biopsy of a pneumoconiosis patient exposed to Sb_2O_3. It should be noted that no abstract was included in the bibliography regarding this reference. Considering that this paper[4] by Li et al is only a case report

(https://pubmed.ncbi.nlm.nih.gov/18724902/) we believe the omission of this paper will not affect the overall conclusion of this systematic review.
    - Of the 10[2,5,6,14,15,35,36,44,52,54] studies that were thought to be relevant and were retrieved in full, eight[2,5,14,15,36,44,52,54] studies did not provide any new data, were not relevant to the objective of this systematic review or were in the form of expert reviews that were traced for their relevant primary studies. Hence, these eight[2,5,14,15,36,44,52,54] studies will not be discussed further.
    - Ten[63-72] further studies were identified from manual searches. Of these 10[63-72] studies, two[64,68] studies were in the form of expert reviews (level of evidence 5. Appendix 1) in which we traced for their relevant primary studies and found that those primary studies were already identified in our search or were included in other systematic reviews, such as those of the Agency for Toxic Substances and Disease Registry (ATSDR)[71] or IARC[72] and will not be discussed further.
    - The website of the International Antimony Association (i2a) (https://www.antimony.com/library/) provided some publications. As we examined these publications, we did not find any relevant data to the objective of this systematic review. Hence, none of the available documents in the i2a library (https://www.antimony.com/library/) will be discussed.
    - Overall, there were 10[6,35,63,65,66,67,69,70,71,72] studies appraised and summarized in this systematic review.

- A small (n=51) case series (level of evidence 4. Appendix 1) reporting on antimoniosis, a special form of pneumoconiosis, among workers in an antimony smelting plant exposed to the airborne dust containing a high concentration of Sb_2O_3 (up to 88 %) and Sb_2O_5, was reported by Potkonjak and Pavlovich[6]. Fifty-one males who worked as smelters in the smelting plant, aged between 31- 54 years old (mean age 45.2), were exposed to dust containing predominantly antimony oxide and had definitively experienced pneumoconiotic changes. These workers had been working in the factory from 9-31 years (mean 17. 9 years). Lung X-ray findings across time demonstrated antimoniosis which were characterized by the presence of diffuse, densely distributed punctate opacities, which were round or polygonal, irregular in shape and had a diameter usually less than 1.0 mm and were concentrated particularly in the mid-lung fields. Chronic coughing was recorded in 60.8 % cases; conjunctivitis was reported in 27.5% of cases and upper airway inflammation in 35.3% of cases. Antimony dermatosis was present in 62.7% of cases and was observed especially during the summer season. Extensive pulmonary function testing did not reveal any specific pattern. Further, chronic bronchitis defined (as chronic persistent or recurrent coughing with expectoration lasting three months each for two consecutive years) was found in 37.3 % of cases; chronic emphysema, based on x-ray and pulmonary function evidence of hyperinflation was found in 34.5 %; inactive tuberculosis in 18.2 % and pleural adhesions in 27.3 % cases. No malignant lesion was detected in these cases. *It should be noted that it was not clear how these patients were selected in this presentation; exposure to silica was also present in this worker; there was no information other respiratory risk factors (such as smoking) were explored in this case series. It should also be noted that there was no level of exposure data presented in this series.*
- A relatively good quality (*clear objective, clear literature search criteria, employing certain checklist for critical appraisal with clear data presentation and relevant conclusion*) systematic review (level of evidence 1. Appendix 1), with literature search date of June 2018, was presented by Saerens et al[35]. Concerned with potential carcinogenic effects of Sb_2O_3 in humans as a response to the 2018 National Toxicology Program (NTP) Report on Carcinogens Monograph on Antimony Trioxide[73] which concluded that there was sufficient evidence of the carcinogenicity of Sb_2O_3 in experimental animals, Saerens et al conducted this systematic review with an emphasis on data available in workers. *It should be noted*

that an updated (2021) NTP report on carcinogens c.q. on Sb_2O_3 *was included in this EBPG systematic review*[44]. In their systematic review, Saerens et al[35] concluded that evidence of antimony carcinogenicity in workers (*human*) was inadequate. The authors identified the unexplained role of other exposures, such as arsenic as well as smoking in the primary studies; the potential effect of small sample sizes; heterogeneity in industries involved in the primary studies; heterogeneity in the exposure dose as well as on the duration of exposures. The authors also emphasized the incomparability across primary studies which examined multiple organs and multiple substances with inadequate reference populations. Within this limitation, the authors concluded that Sb_2O_3 carcinogenicity in workers is probable (International Agency for Research on Cancer (IARC) category 2A) The authors emphasized the fact that the lack of clarity on the occupational exposure duration and the dose on which the effect arose and whether exposure threshold values should be reconsidered. *It should be noted that a more recent, 2023, IARC publication on antimony discussed in this systematic review*[72] *also came to the conclusion that antimony is classified as category 2A with regard to cancer in humans. The IARC findings will be discussed further*.

- In their chapter on antimony (*this chapter is a form of expert review hence is considered as level of evidence 5. Appendix 1*), Tylenda et al[63] summarized human health effects of antimony. The authors reported on:
    - Gastrointestinal effects as a results of acute antimony poisoning generally manifested as vomiting, nausea and diarrhea.
    - Acute respiratory exposure to antimony trichloride causing irritation and soreness of the upper respiratory tract. The reported exposure level was at 73 mg/m^3.
    - Chronic respiratory effects including rhinitis, pharyngitis, pneumonitis, tracheitis, soreness in the nose and nosebleeds. The reported level of exposure ranged from 4.7 to 11.8 mg/m^3. Tylenda et al also emphasized the potential role of co-exposure to arsenic oxide, hydrogen sulfide, iron oxide, and sodium hydroxide in these cases. The authors also reported on antimoniois as described previously[6].
    - Pustular skin eruptions known as antimony spots that may be seen in individuals working with antimony and antimony salts. These eruptions were transient and mainly affect skin areas exposed to heat and those areas where sweating occurs. The authors did not provide any data on the exposure level.
    - Other health effects such as on the circulatory system, immunological effects as well as hemolytic effects were also reported but it was associated with other types of antimony such as antimony trisulfide or SbH_3 gas.
- A large (n=1420) retrospective cohort study (level of evidence 3. Appendix 1) investigating mortality of antimony workers, during the period of 1961-1992, among antimony smelter workers in northeast of England, was reported by Jones[65]. All employees in the company employed on January 1, 1961, were recruited into the study. The study was limited to men with at least three months employment and for the purpose of analysis the data was then categorized into four occupational groups including antimony workers, maintenance workers, zircon workers and others that included office workers and management staff. Of the 2508 people recruited into the study; 356 of these were females and 700 were males with < 3 months service. Further, vital statistic data of 32 of the 1452 remaining males were not available. Of the 1420 male workers with vital statistic data that became the basis of the analysis, 357 had died and 29 emigrated by the end of December 31, 1992. *It should further be noted that it was clear how many workers were registered during the period of 1961-1992*. The authors reported that for men working on the smelter before 1961 a statistically significant increase in mortality from lung cancer was found (32 observed vs. 14.7 expected, $P < 0.00$). A similar excess was observed among maintenance workers (12 observed v 5.3 expected $P = 0.02$). The authors provided evidence of a minimum latency period of 20 years between first exposure and death from lung cancer. No evidence was

found for a correlation between length of time worked and mortality from lung cancer. *The excess mortality associated especially to lung cancer in these antimony smelter workers has to be interpreted with caution as it was unclear how participants were selected; there was no information on how large the overall population of workers was during the study period of 1961-1992; potential effect of confounders such as co-exposure with arsenic as well as smoking were not explored. It should also be noted that there was no data on the level of exposure to Sb_2O_3 presented in this study.*

- Another large (n=1462) retrospective cohort study (level of evidence 3. Appendix 1) investigating lung cancer mortality at a UK tin smelter was reported by Jones et al[66]. The Capper Pass smelter, from which participants were recruited, took process residues from other smelters, together with some raw ores, as feedstock. The main process of this smelter comprised raw materials handling, feed mixing and drying, sintering and reduction in a blast furnace to produce an impure alloy of tin and lead. In the process workers were exposed to metal alloys such as lead, antimony, arsenic, cadmium as well as 210 Polonium. Air sampling, area and individual, data were available from the period of 1972-1991. Overall, there were 35,942 person-years at risk for the 1462 workers accumulated for data analysis. The authors presented an unweighted as well as weighted (for time since exposure and age) regression of lung cancer mortality in association with exposure to lead, antimony, arsenic, cadmium as well as 210 Polonium. Combining all available exposure data, with regard to antimony (*it was not clear what type of antimony, such as Sb_2O_3 or Sb_2O_5 or SbH_3 etc. was detected in these* samples), the authors estimated for exposures 1972-1991 (*this exposure period contained true measured data*), the median exposure level was 0.37 mg year/m^3 while extrapolated exposure data encompassing period of 1937-1991, their median exposures varied from A: 0.59 mg year/m^3, B: 0.62 mg year/m^3 and C: 0.63 mg year/m^3, depending on the assumptions of the data. Significant trends in lung cancer mortality with increasing weighted cumulative exposure to lead, antimony and arsenic were found for all three scenarios of pre-1972 exposure. *It should be noted that it was not clear how participants were selected for this study; it was also not clear how large was the underlying worker population and this study did not explore the effect of co-exposures such as arsenic as well as the potential effect of other confounders, such as smoking, in their statistical model. It should also be noted that numerous statistical tests, without adjustment to the type 1 error level, were presented in this study.*
- A large (n total 5499 with 888 glass workers as "cases") correlational study (level of evidence 4. Appendix 1), investigating occupational cancer due to various metal exposures among glass workers in Sweden, for the years of 1950-1982, was reported by Wingren and Axelson[67]. The authors employed data on the deceased, men ≥ 45 years at the time of their death from a population of eleven parishes covering the glass-producing area in southeast Sweden for the years 1950-1982. This mortality data was then correlated with data on the consumption of different metals, including arsenic, copper, nickel, manganese, lead, chromium, antimony, cadmium, selenium and zinc, in the 1960s. For each of the metals studied, the glassworks were divided into three categories: (1) glassworks consuming no amount of the metal, (2) glassworks consuming small amounts (expressed as kilograms of metal per year and number of employees), and (3) glassworks consuming large amounts of metal. The authors found a decrease in stomach cancer risk that was associated with increased exposure to antimony (*it is not clear what type of antimony was involved in this study*) while an increasing trend in risk of colon cancer was seen. For lung cancer, no obvious trend with any metal could be found. *It should be noted that this is only a correlational study that cannot provide evidence on causality; further this study did not explore the potential effect of co-exposure (such as those or arsenic which had been found in this data to have a high correlation with exposure to antimony) as well being unable to provide data on the level of exposure involved.*

- A small (n=28) retrospective cohort study (level of evidence 3. Appendix 1) reporting on the occurrence of pneumoconiosis among antimony process workers was reported by Cooper et al[69]. Twenty-eight workers, with age ranges of 25-61 years and duration of exposure from 1-15 years participated in this study. Three (10.7%) positive cases of pneumoconiosis and five (17.9%) suspected findings were identified in this study. Fourteen participants who had been exposed to Sb_2O_3 for periods of time from 1 to 15 years were available for pulmonary function studies. However, no specific pattern of lung function abnormalities was identified. *It should be noted that that it was not clear how these participants were recruited; it was not clear the size of the underlying worker population; it was not clear what was the role of co-exposure, especially to silica as well as smoking, in the development of pneumoconiosis in this population. Further, no level of exposure data was presented.*
- A large (n=1014), retrospective, administrative data based, cohort study (level of evidence 3. Appendix 1), investigating the excess mortality from lung cancer, cardiovascular disease or non-malignant respiratory diseases among antimony smelter workers, was reported by Schnorr et al[70]. Participants were recruited from an antimony smelter in southern Texas who were hired between January 1, 1937, and July 1, 1971 and were employed for a minimum of three months. There were 91 white, and 923 Spanish-surnamed males included in this study (*it is not clear how big was the underlying population and how these workers were selected for this study. The authors mention excluding females (n=17) and non-white males (n=21) from the analysis*). No exposure data were available from 1930-1974 and the researchers relied on two industrial hygiene surveys conducted by the US NIOSH in 1975 and 1976 for their exposure data across the study time frame. The geometric mean of antimony levels of twelve area samples taken in 1975 and fifty personal samples taken in 1976 were 551 $\mu g/m^3$ and 747 $\mu g/m^3$, respectively. It should be noted that exposure to arsenic was also detected in these two sampling periods. The 1014 workers included in this analysis yielded 33,733 person years at risk with mean age at employment of 32 years old, mean length of employment 6.8 years and mean length of follow-up 35 years. The authors calculated that the overall cancer mortality was slightly lower compared to US population in general (standardized mortality rate (SMR) 0.88; 95% confidence interval (CI): 0.72-1.06). With regard to those exposed to antimony, significant elevation in mortality from liver cancer (SMR: 3.17; 95% CI:1.27-6.52) was detected when compared to US white males. Those exposed to antimony also showed non-significant deficit in emphysema and bronchitis death (SMR:0.59) and slight elevation of death from influenza and pneumonia (SMR:1.23) as well as nonsignificant increase in death due to pneumoconiosis/other respiratory diseases (SMR:1.22; 90% CI:0.80-1.80). The authors acknowledged that the observed increased in SMR might be due to confounders effect.
- In 2019, the US Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA) published and updated version of their 2017 toxicological profile of antimony[71]. Based on high quality (*clear objective, clear search strategy, critically appraising primary studies, clear results presentation*) systematic review (level of evidence 1. Appendix 1), with regard to human health effect, the ATSDR concluded that:

    - Toxic side effects in humans following intraperitoneal, intravenous, or intramuscular injection of an antimony-containing drug had been reported, including altered electrocardiograms (EKGs), vomiting, diarrhea, and joint and/or muscle pain. These side effects were more frequently observed following administration of trivalent antimony compounds, especially antimony potassium tartrate or antimony sodium tartrate; side effects have also been found in humans administered pentavalent organic compounds such as sodium antimony gluconate or meglumine antimoniate.

- Adverse health effects had also been reported in humans following inhalation, oral, or dermal exposure to antimony and antimony compounds. These studies predominantly assessed the toxicity of trivalent antimony compounds, particularly antimony trioxide and antimony potassium tartrate. ATSDR further concluded that:
    - Respiratory effects following inhalation exposure are a presumed health effect for humans based on low-level low-quality evidence in workers exposed to antimony oxides and a high level of evidence in several animal species exposed to antimony trioxide, antimony trisulfide, and antimony ore. The respiratory effects include irritation of epiglottis epithelium, increases in the number of alveolar/bronchiolar macrophages, decreases in lung clearance, and lung interstitial fibrosis.
- The lowest observed adverse effect levels for respiratory tract effects following acute, intermediate, and chronic duration exposures are 12 mg Sb/m3 as Sb_2O_3, 4.11 mg Sb/m3 as Sb_2O_3, and 1.6 mg Sb/m3 as Sb_2O_3, respectively.
    - Myocardial effects and EKG alterations are a suspected health effect for humans based on inadequate evidence in an inhalation occupational exposure study and low evidence in inhalation and oral exposure studies in animals. This hazard identification conclusion is supported by numerous reports of cardiovascular effects in patients administered antimony compounds for the treatment of leishmaniasis and injection studies in animals.
    - Gastrointestinal effects are a presumed health effect for humans based on inadequate evidence in human studies and high evidence in animal studies. Observed gastrointestinal effects include nausea and vomiting and forestomach ulceration.
    - Developmental effects are a suspected health effect for humans based on inadequate evidence in humans and high evidence in a small number of animal studies. Developmental effects observed in laboratory animals included decreases in pup growth and alterations in vasomotor reactivity in pups.
    - Alterations in blood glucose levels are a suspected health effect for humans based on high evidence from two animal oral exposure studies, supported by an animal intramuscular exposure study; human data are lacking.
    - With regard to mortality (in human), so far, studies were not adequate to establish a relationship between antimony and death.
    - Cancer: several primary studies of antimony oxide workers have examined the carcinogenic potential of antimony. *It should be noted that primary studies[65,70] on workers exposure were identified and appraised in the EBPG systematic review.* ATSDR quoted that the US National Toxicology Program (2018) categorized Sb_2O_3 as reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from experimental animal studies and supporting mechanistic data. IARC (2015) has determined that Sb_2O_3 was possibly carcinogenic to humans (Group 2B) and antimony trisulfide was not classifiable as to carcinogenicity in humans (Group 3).

- The IARC updated publication on antimony[72], published in 2021, concluded that, with regard to cancer in humans, there was limited evidence in humans for the carcinogenicity of trivalent antimony. Positive associations have been observed between exposure to trivalent

antimony and cancer of the lung. There was inadequate evidence in humans regarding the carcinogenicity of pentavalent antimony. IARC further categorized trivalent antimony as "probably carcinogenic to humans" (Group 2A) and pentavalent antimony as "not classifiable as to its carcinogenicity to humans" (Group 3). *Notice the updated category from Group 2B in 2015 to Group 2A in 2021 for trivalent antimony*. The argument presented for Group 2A classification was based on limited evidence for cancer in humans, sufficient evidence for cancer in experimental animals, and strong mechanistic evidence. With regard to exposure to trivalent antimony to cause lung cancer in humans, IARC stated that there was limited evidence, and the main evidence came from three[66,67,70] occupational cohort studies among antimony- or tin-smelter workers that the EBPG appraised previously.

- It should be noted that the revised TLV proposed by ACGIH in 2019 (0.02 mg inhalable Sb/m³) was calculated by transforming the lowest concentration of respirable antimony trioxide of the 2018 NTP[73] studies' mice and rats that developed adverse chronic lung effects (3 mg Sb/m³) into a human equivalent concentration, and further dividing it by several uncertainty factors. Very little detail was provided regarding the conversion in which respirable aerosol impacts in the NTP studies were converted to a proposed inhalable limit or the uncertainty factors that were applied in ACGIH's derivation of the proposed TLV[1].

Summary

- At present, there is some evidence, mainly coming from low-medium quality low-medium level of evidence, on the human health effects with regard to exposure to Sb_2O_3. The health effects identified so far included respiratory effects (irritation of epiglottis epithelium, increases in the number of alveolar/bronchiolar macrophages, decreases in lung clearance and pneumoconiosis), myocardial effects and EKG alterations as well as gastrointestinal effects (nausea, vomiting and forestomach ulceration).
- With regard to lung cancer, the available evidence on human studies had to be interpreted with caution due to the fact that bias (especially those associated with selection and exposure measurement bias), chance (due to multiple comparison) and unaccounted effect of confounding (especially those of smoking status and co-exposure to arsenic) cannot be discounted in affecting the observed outcomes.
- On the occupational level of exposure associated with these health effects, to this date, the exposure was higher than the recently proposed ACGIH TLV of 0.02 mg/m^3 inhalable particulate matter.

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Appendix 1

WorkSafeBC — Evidence-Based Practice Group levels of evidence (adapted from 1-6)

1	Experimental, randomized controlled trial (RCT), systematic review RTCs with or without meta-analysis.
2	Evidence from controlled trials without randomization (quasi-experimental studies) or systematic reviews of observational studies.
3	Evidence from cohort or case-control analytic studies, preferably from more than 1 centre or research group.
4	Evidence from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments.
5	Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees based on scientific evidence.

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