

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Cancer incidence among Finnish ferrochromium and stainless steel production workers in 1967-2011
AUTHORS	Huvinen, Markku; Pukkala, Eero

VERSION 1 - REVIEW

REVIEWER	Antero Aitio Finnish Institute of Occupational Health, retired Finland
REVIEW RETURNED	16-Sep-2013

GENERAL COMMENTS	<p>This is a carefully planned and executed study in ferrochromium/stainless steel production, where published studies are somewhat contradictory. The follow-up is complete, and the incident cases have been identified from a cancer registry with proven reliability. Although smoking data seem to be available only as prevalence numbers in the cohort and among the referents, and the mean follow-up time is only 24.1 years, and the accumulated person years in the different exposure categories was rather small, the finding of no increased cancer, and specifically lung and cancer is apparently reliable and demonstrates that when a process with low Cr6 exposure is applied, cancer risk does not seem to be a problem.</p> <p>There are some points that the authors could clarify, as follows:</p> <p>A key part of the study is the description of exposure, and this is unfortunately quite brief: medians and maximal exposures for total dust, chromium and Cr6 are given, but it would be quite important to indicate, how well these figures represent the exposure over the time of the study, from 1967 to 2004. How many measurements, how well did these cover the whole exposure period?</p> <p>AS with all lung cancer studies, tobacco smoking is the most important potential confounder. In the discussion section, information on is given of smoking prevalence; the ways in which this information was obtained, should be explained in the methods section.</p> <p>There is now a robust estimate of the potency of Cr6 as lung carcinogen in humans (Gibb HJ, Lees PS, Pinsky PF, Rooney BC (2000) Lung cancer among workers in chromium chemical production. American journal of industrial medicine, 38:115-126, Park RM, Bena JF, Stayner LT, Smith RJ, Gibb HJ, Lees PS (2004) Hexavalent chromium and lung cancer in the chromate industry: a quantitative risk assessment. Risk analysis, 24:1099-1108. It would be quite interesting to assess how well the present negative findings fit with that model.</p>
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	<p>Page 7, lines 12-18: The exposure decreased "at a rate of 17%". Is this the overall decrease from 1970 to (an unspecified point of time in) to the 1990s or a rate of decrease annual? per decennium?</p> <p>Page 8, line 7: For an uninitiated reader, the "limit level given by the national radiation authorities" is not informative. What was this limit (and was it the same over the study period). How frequently was the radiation dose estimated = how well is it established that the radiation exposure really was low.</p> <p>Page 12, lines 10-26: I wonder if it would be more specific with regard to the tobacco confounding: this is an essentially negative study, so the differences in smoking habits could only be important as negative confounding – and the smoking figures are even stronger to refute this concept (than the possibility of positive confounding).</p> <p>Page 13, lines 28-37: I fail to see how intensified screening for prostate cancer could affect the SIR – why would the increased detection be different in the cohort as opposed to the referent population?</p>
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REVIEWER	BOURGKARD Eve Institut National de Recherche et de Sécurité (INRS), France
REVIEW RETURNED	24-Sep-2013

GENERAL COMMENTS	<p>Number 2 - ABSTRACT: In the method section, please specify the follow up period for incidence. In the result section(L37, 39, 41), the words "decrease", "increase" are not suitable. "Increase", for instance, means to become greater or larger. In that case, incidence doesn't increase but is higher than reference. Please use expressions: "lower than reference", "higher than reference". In the conclusion section, the authors should specify that these results correspond to their study. (In our study, ...)</p> <p>Number 6 - STUDY DESIGN Please specify the International Disease Classification codes used for the cancer cases.</p> <p>Number 10 - In the discussion section, such as in the abstract, please replace "decreased", "increased" by "lower than reference", "higher than reference", expressions more suitable (For example, P10 L5, L7, L14, L33).</p> <p>P5 L30: Is it possible to locate geographically the mine and the production units and compared them to the place of the reference population ?</p> <p>P7 L12-18: There has been few changes in exposure levels over time. Is it possible to study SIR for 2 periods of time (for example) ?</p> <p>p18 Table 1: What is "Department" ? Department of hire ?</p> <p>p8: Why did the author analyse men and women together ? Do they do the same job ?</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

1. A key part of this study is the description of exposure, and this is unfortunately quite brief: medians and maximal exposures for total dust, chromium and Cr6 are given, but it would be quite important to indicate, how well these figures represent the exposure over the time of the study, from 1964 to 2004. How many measurements, how well did these cover the whole exposure period?

Response: The figures indicated in our study are based on previously published studies from the same production chain. We corrected the paragraph on page 7 as follows: “The exposure levels described above represent typical working conditions during normal production operations. The continuous monitoring system for dust exposure including several thousands of samples has shown that the concentrations of chromium-containing dusts in the workplace air decreased at an annual rate of 17% from 1970 to the early 1990s in the mine, the ferrochromium works and the stainless steel melting shop. In the cold rolling mill, the concentrations have always been very low.”

2. As with all lung cancer studies, tobacco smoking is the most important potential confounder. In the discussion section, information is given of smoking prevalence; the ways in which this information was obtained, should be explained in the methods section.

Response: We have now added a new paragraph on smoking history in the methods section (last paragraph before Results section, page 8) as follows: “Smoking habits of a representative sample of the employees were documented by questionnaires in connection with two identical cross-sectional respiratory health studies in 1993 and 1998.[8] This information was received for all except one of the 222 employees with at least eight years in the same department (chromite mine, ferrochromium plant, stainless steel melting shop, or annealing and pickling lines of the cold rolling mill).”

3. There is now a robust estimate of the potency of Cr6 as lung carcinogen in humans (Gibb HJ, Lees PS, Pinsky PF, Rooney BC (2000) Lung cancer among workers in chromium chemical production. American Journal of Industrial Medicine, 38:115-126; Park RM, Bena JF, Stayner LT, Smith RJ, Gibb HJ, Lees PS (2004) Hexavalent chromium and lung cancer in the chromate industry: a quantitative risk assessment. Risk Analysis, 24:1099-1108). It would be quite interesting to assess how well the present negative findings fit with that model.

Response: We have added a new paragraph in the discussion section: “A linear trend of increasing risk of lung cancer mortality with increasing cumulative exposure to water-soluble hexavalent chromium containing dusts and mists was observed in a cohort study from a US chromate production plant.[25] Total cumulative exposures to hexavalent chromium in the US plant averaged 0.13 mg/m³-years (as CrO₃), with a maximum value of 5.3 mg/m³-years. In our study the estimated cumulative exposures at the stainless steel melting shop were lower; the median cumulative exposure was 0.034 mg/m³-years (as CrO₃) and the theoretical maximum value based on peak exposure levels was 0.44 mg/m³-years .”

Hence, our negative findings fit well with that model: the theoretical maximum cumulative exposures, which are based on occasional peak values, are in our study essentially lower than the cumulative exposures in the US chromate production study.

4. Page 7, lines 12-18: The exposure decreased “at a rate of 17%”. Is this the overall decrease from 1970 to (an unspecified of time in) to the 1990s or a rate of decrease annual? Per decennium?

Response: The given rate was an annual rate. We have reworded the sentence “at an annual rate of 17%”.

5. Page 8, line 7: For an uninitiated reader, the “limit level given by the national radiation authorities” is no informative. What was the limit (and was it the same over the study period). How frequently was the radiation dose estimated = how well is it established that the radiation exposure really was low.

Response: The annual personal dose limit has been 1 mSv for the past decades. We have changed the text on page 8 as follows: “...Since the beginning of production at the stainless steel melting shop

in 1976 there has been 13 identified incidents with americium contamination. In the individual measurements conducted after accidental and occasionally occurring exposures only one personal radiation dose has, however, exceeded the safety limit of 1 mSv per year given by the national radiation authorities.”

6. Page 12, lines 10-26: I wonder if it would be more specific with regard to the tobacco confounding: this is an essentially negative study, so the differences in smoking habits could only be important as negative confounding – and the smoking figures are even stronger to refute this concept (than the possibility of negative confounding).

Response: We agree with the argument and we therefore added in discussion a statement “...and the smoking figures rather point towards a negative confounding” (second last paragraph under header Lung cancer).

7. Page 13, lines 28-37. I fail to see how intensified screening for prostate cancer could affect the SIR – why would the increased detection be different in the cohort as opposed to the referent population?

Response: We now explain this issue more carefully: “PSA testing in the Nordic countries started in the 1990s in Sweden, and in Finland it first became common in the Tornio region next to Swedish border[31]. The incidence of prostate cancer has therefore been higher in the area around Tornio Works than in the rest of the reference area. This high regional PSA testing activity may well have lead to an elevated incidence of prostate cancer diagnoses among the cohort members compared to the reference population.”

Reviewer 2:

1. Abstract. In the method section, please specify the follow up period for incidence.

Response: We have added “until 2011” in the method section.

2. In the result section (L37, 39, 41), the words “decrease”, “increase” are not suitable. “Increase”, for instance, means to become greater or larger. In that case, incidence doesn’t increase but is higher than reference. Please use expressions: “lower than reference”, “higher than reference”.

Response: We have replaced all through the text “increased” by “elevated” and “decreased” by “lowered”.

3. In the conclusions section, the authors should specify that these results correspond to their study. (In our study, ...)

Response: We have revised the sentence “As a conclusion, the exposure levels in our study are low, and ...”.

4. Number 6 – STUDY DESIGN Please specify the International Disease Classification codes used for the cancer cases.

Response: As suggested by the reviewer, we added the following specification: “The Finnish Cancer Registry uses International Classification of Diseases for Oncology, third edition (ICD-O-3) in coding of topography and morphology of malignancies.”

5. Number 10 – In the discussion section, such as in the abstract, please replace “decreased”, “increased” by “lower than reference”, “higher than reference”, expressions more suitable (For example, P10 L5, L7, L14, L33).

Response: We have replaced all through the text “increased” by “elevated” and “decreased” by “lowered”.

6. P5, L30: Is it possible to locate geographically the mine and the production units and compare them

to the place of the reference population?

Response: We have defined the location adding a sentence "Tornio Works are located in the Western part of the reference area, on the coast of the Baltic Sea at the Swedish border."

7. P7 L12-18: There has been few changes in exposure levels over time. Is it possible to study SIR for 2 periods of time (for example)?

Response: The SIRs were also studied separately for several calendar periods. There were no significant differences in SIRs between the periods. We added a paragraph in the end of Result section: "The analyses were also stratified by calendar period (to indicate possible effect of decreasing trend in exposure levels) and sex (to indicate the possible different relative risk between men and women with similar exposure). There were no significant differences between the period- or sex-specific SIRs."

8. P18 Table 1: What is "Department"? Department of hire?

Response: We now indicate in the title of Table 1, that we speak about department of hire.

9. P8 Why did the author analyse men and women together? Do they do the same job?

Response: The proportional share of men and women in various departments does vary, but there are, for example, several female miners, who perform exactly the same job tasks as their male colleagues. Exposures are department specific with practically no differences due to sex of the employees. There were no significant differences between the sex specific SIRs in any of the departments. We added a paragraph in the end of Result section: "The analyses were also stratified by calendar period (to indicate possible effect of decreasing trend in exposure levels) and sex (to indicate the possible different relative risk between men and women with similar exposure). There were no significant differences between the period- or sex-specific SIRs."