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The opinion of the Italian Society of Occupational Medicine and Industrial Hygiene (SIMLII) on silica-exposure and lung cancer risk

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Key words
Silica; silicosis; lung cancer

Summary
Background: *The Italian Society of Occupational Medicine and Industrial Hygiene (SIMLII) began a thorough overview of the silica-silicosis-lung cancer question starting in 2005.* **Methods and Results:** *The body of information obtained from a number of epidemiological studies, meta-analyses and reviews following the decision of the IARC to classify Respirable Crystalline Silica (RCS) as a human carcinogen (Group 1) led to different conclusions, which can be summarized as follows: basically an increased risk of developing lung cancer is demonstrated and generally accepted for silicotics; the association of lung cancer and exposure to silica per se is controversial, with some studies in favour of an association and some leading to contrary conclusions. Due to methodological problems affecting most studies and the difficulty in identifying the mechanism of action, we agree that the silica-lung cancer association is still unclear. The UE approach is more practical than scientific, in that it recommended the use of "good practices" subject to an agreement with the social partners, without any need to classify RCS as a human carcinogen. However, in 2008 the UE asked the Institute of Occupational Medicine (IOM) in Edinburgh to assess, as a primary objective, the impact of introducing a system for setting Occupational Exposure Limits (OELs) based on objective risk criteria.* **Conclusion:** *In the present state of the art SIMLII's conclusions are: a) There is no need to label RCS with phrase H350i (ex R.49); b) It is of utmost importance to enforce compliance with current OELs; c) Future guidelines specific for silicosis risk should include adequate health surveillance; d) For legal medicine purposes, only lung cancer cases with an unquestionable diagnosis of silicosis should be recognised as an occupational disease.*

Riassunto
«Il punto di vista della Società Italiana di Medicina del Lavoro e Igiene Industriale (SIMLII) su esposizione a silice e rischio di tumore polmonare». *La relazione silice-silicosi-tumore del polmone è stata valutata approfonditamente dalla Società Italiana di Medicina del Lavoro e Igiene Industriale (SIMLII) dal 2005 in poi. L'insieme dei dati ottenuti mediante numerosi studi epidemiologici, meta-analisi e revisioni dopo la decisione della IARC di classificare la Silice Libera Cristallina (SLC) quale carcinogeno umano (Gruppo 1) ha portato a diverse conclusioni che possono essere riassunte come segue: un aumento di rischio per il tumore polmonare è dimostrato e generalmente accettato per i silicotici; in assenza di silicosi l'associazione tumore del polmone e SLC è controversa, essendovi in*

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letteratura studi che depongono a favore di tale associazione ed altri che la negano. In considerazione dei problemi metodologici presenti in molti studi e la difficoltà di individuare un meccanismo d'azione, siamo del parere che l'associazione tumore e SLC di per sé sia tuttora non chiarita. L'Unione Europea ha affrontato il problema in modo più pratico che scientifico in quanto ha raccomandato l'uso delle "buone pratiche", previo accordo tra le parti sociali, senza alcuna necessità di classificare la SLC quale carcinogeno umano. Tuttavia, ha richiesto all'Istituto di Medicina Occupazionale di Edimburgo (IOM) di valutare, quale primo obiettivo, l'impatto dell'introduzione di un sistema per stabilire Limiti di Esposizione Occupazionale (OEL) basato su criteri di rischio obiettivi. All'attuale stato dell'arte le conclusioni della SIMLII sono: a) Non vi è necessità di etichettare la SLC con la frase H350i (ex R.49); b) È di primaria importanza il rispetto degli attuali standard ambientali; c) Future linee-guida specifiche per la silicosi devono comprendere adeguata sorveglianza sanitaria; d) Per scopi medico-legali solo i casi di tumore del polmone con diagnosi certa di silicosi dovrebbero essere considerati di origine occupazionale.

Premise

In a Congress held in Florence in September 2005 Enrico Pira represented the Italian Society of Occupational Medicine and Industrial Hygiene (SIMLII) in a Round Table discussion on the epidemiological evidence of the adverse effects of silica exposure (22).

In the same year Giorgio Piolatto presented the SIMLII "Working Document" on silica and lung cancer at the SIMLII National Congress held in Parma (21).

The present report consists of an update of the SIMLII viewpoint on the silica-silicosis-lung cancer question.

Background

The somewhat controversial decision of the International Agency for Research on Cancer (IARC) to classify Respirable Crystalline Silica (RCS) as a human carcinogen (Group 1) in 1997 (11) was followed by a proliferation of epidemiological studies in various industrial settings, meta-analyses and reviews leading to different conclusions (with some indicating an increased risk of developing lung cancer following silica exposure, some indicating no association with exposure to silica *per se* and some indicating an association only in presence of silicosis).

This is not unusual in medical science, where conflicts do arise quite often between old views and further evidence from new data, but it is of overwhelming importance when regulatory Agencies or similar Institutions are called to give "official" opinions and recommendations for use by Governments in issuing laws, directives or simply guidelines.

Due to editorial requirements, this paper will not include the results of animal experiments and it is not intended to examine in depth all published epidemiological studies, but rather it will consist of an evaluation of the most reliable reports (in our opinion) summarizing the available literature through pooled analyses and meta-analysis, reviews and comments on the state of the art of the silica-silicosis-cancer question. The position of Institutions aimed at giving practical indications on the issue will also be taken into account.

The epidemiological evidence

The IARC multicentre study (24) represented, with 10 cohorts and about 66.000 workers (mainly Chinese miners and pottery workers), "the largest existing body of data for determining an exposure-response analysis for silica and lung cancer". The results tended "to support the conclusion by the IARC that inhaled crystalline silica in occupational settings is a human carcinogen". We presume that the aim of the authors was to carry out a research that, due to the magnitude of the global cohort and the effort to accurately estimate past exposures, should have been considered as a pivotal investigation able to put an end to the debate. This view was shared by another author (12) who stated that

"lung cancer should now be definitively added to the list of silica's toxic effects". However, there are some limitations of the study by Steenland et al., such as the fact that the authors did not exclude silicotic patients "which if removed from the analysis might have resulted in a lower risk estimate *(3)*". There was also considerable heterogeneity across the cohorts in the results of internal analysis, where the criteria of inclusion or exclusion of large strata of the global cohort are not fully explained [e.g., surface miners were considered as unexposed because a minimum exposure level of 0.01 mg/m^3 was assigned to them (!?)]. Finally, we share the opinion of Brown and Rushton (3) that "the shallow exposure-response relationship is hard to interpret".

Furthermore, a case-control study (4) nested in 3 cohorts of Chinese miners and pottery workers, in which the effect of co-exposures (arsenic, PAHs, radon and smoking) was included in the analysis, showed that the data did "not provide any evidence to show that exposure to silica causes lung cancer in the absence of confounding factors".

Nonetheless, a IARC Working Group reaffirmed (25) the carcinogenicity of crystalline silica dust only on the basis of the study by Steenland et al. (24). The established mechanistic event was "impaired particle clearance leading to macrophage activation and persistent inflammation" which, incidentally, is the mechanism of the onset of silicosis and not that of lung cancer.

Kurihara et al (13) selected 30 studies (17 cohort and 13 case-control studies) published between 1966 and 2001 in order to evaluate the lung cancer risk in silicotics and non-silicotics. The pooled Risk Ratio (RR) for all studies was 1.32 (95% CI 1.23-1.41). In the same investigations the pooled RR was 2.37 (95% CI 1.98-2.84) in silicotics only (based on 16 studies), whereas no increase in risk emerged in non-silicotics (pooled RR 0.96, 95% CI 0.81-1.15, based on 8 studies). The authors concluded that silica may induce lung cancer indirectly, probably through silicosis.

Pelucchi et al (20) carried out a systematic review of epidemiological investigations on silica-silicosis lung cancer risk published after the IARC Monograph (11). The meta-analysis included 28 cohort, 15 case-control and two Proportionate Mortality Ratio (PMR) studies. The pooled RRs of lung cancer, calculated using random effect models were 1.34 (95% CI 1.25-1.45) for all cohort studies and 1.41 (95% CI 1.18-1.67) for all case-control studies. However, different patterns emerged according to different studies and subcategories. The pooled RRs were 1.69 (95% CI 1.32-2.16) in cohort studies and 3.27 (95% CI 1.32-8.2) in case-control studies of silicotics, 1.25 (95% CI 1.18-1.33) in cohort studies and 1.41 (95% CI 1.18-1.70) in case-control studies where silicosis status was undefined and 1.19 (95% CI 0.87-1.57) in cohort studies and 0.97 (95% CI 0.68-1.38) in case-control studies of non-silicotics.

The conclusions were that the association with lung cancer was consistent for silicotics, but the data were limited for non-silicotics (2 studies only) and not easily explained for workers with undefined silicosis status (who represented the largest body of data in the whole meta-analysis), thus leaving open the issue as to whether silica *per se* materially increases lung cancer risk in absence of silicosis. The authors also highlighted several limitations affecting risk estimates in most studies (namely: the use of national vs. local rates as reference, controlling for smoking, the possibility of stratifying the analysis according to silicosis status, co-exposures to other lung carcinogens, past exposure assessment, dose-response relationships and sometimes the authors' interpretation of their own findings). Some of these limitations were also reported by Brown and Rushton (3), especially insofar as past exposure assessment is concerned.

Two subsequent studies were published by Lacasse et al (14, 15). The first (15) was focused on the silicosis-cancer association and consisted of a meta-analysis of 31 studies (27 cohort studies and 4 case-control studies). The pooled SMR for lung cancer mortality after adjustment for smoking was 1.60 (95% CI 1.33-1.93).

The authors concluded that "… there is nevertheless evidence, from data restricted to never-smokers" and from a "dose-response analysis, that silicosis and lung cancer are associated". A further remark was "this association does not necessarily imply that silica is a lung carcinogen".

The second study (15) points to different conclusions and is more difficult to interpret. The meta-analysis comprised 10 studies (4 cohort studies and 6 case-control studies which met the inclusion criteria because they reported the results of dose-response analyses after adjustment for smoking). The finding of an increasing lung cancer risk with increasing cumulative exposure to silica led the authors to the following conclusion: "Silica is a lung carcinogen. The increased risk is particularly apparent when the cumulative exposure to silica is well beyond that resulting from exposure to the recommended limit concentration for a prolonged period of time".

The question (authors' note) now is: is that cumulative exposure level the one able to induce silicosis too? This doubt is quite obvious since a final remark by the authors was "the interpretation … is however limited by … the confounding effect of silicosis that cannot be fully assessed". Some criticism was also expressed by Morfeld (17) about the choice of the reference exposure level, the level with a RR of 1 [for more information see full text and the reply of Lakhal and Lacasse (16)].

In the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines the authors (1) simply state: "The evidence on silica exposure, absent consideration of the presence of silicosis is less clear. In 1997, the IARC did classify crystalline silica as a human carcinogen; however, some still continue to question its carcinogenicity and the role of silica exposure vs. that of fibrosis in people with silicosis".

The study of Erren et al (8) gave results which look similar (although they do not agree) to those of Pelucchi et al (20). In fact, in the pooled analysis of silicotics (38 eligible studies until 1/2007) the RRs averaged 2.1 (95% CI 2.0-2.3 on fixed effect model, 1.9-2.3 on random effect model). The scantiness of studies on silica-exposed individuals without silicosis was noted also by these authors (only 3 studies with data allowing adjustment for smoking). In this case the pooled risk estimate was 1.0 (95% CI 0.8-1.3). They suggest that "perhaps silicosis is a biomarker of susceptibility" and that there is a need for further research "with time-dependent information on silicosis and on silica dust" as well as for the application of "relatively unfamiliar, but powerful, statistical procedures (like G-estimation) to unravel the complexities of the observational data" and "to answer the important public health question: is silicosis a necessary condition for the elevation of silica-associated lung cancer risk?".

In an in-depth review Brown (2) stated that "If silicosis were the necessary step leading to lung cancer, enforcing the current silica standards would protect workers against lung cancer risk as well. Alternatively, a direct silica-lung cancer association that has been suggested implies that regulatory standards should be revised accordingly". In conclusion: "Further research is needed in order to understand the complex pattern of interactions leading to lung cancer among silica-exposed workers".

A contemporary report of Brown and Rushton (3), commissioned by EUROSIL to answer a number of questions is a 172-page review which comprises the largest number of studies and was aimed at an evaluation of the association of silica not only with lung cancer but also with COPD and NMRD, silicosis, cancers other than lung and autoimmune diseases. As far as lung cancer is concerned it is difficult to summarize the complex conclusions of the authors, also because we do not agree with their interpretation of the results of some studies, such as those by Kurihara (13), Chen (4) and especially the one by Pelucchi (20) in which the authors of the present paper were co-authors.

However, some points are correctly addressed, such as the common statement that "few studies have investigated the risk in relation to RCS-exposed individuals in the absence of silicosis". In general they support the weight of evidence "which also indicates that increasing exposure to RCS" increases lung cancer risk, but "the form and magnitude of the RCS-lung cancer exposure-response relationship varies depending on the industry and the choice of statistical model applied to the data; it is particularly unclear in the low exposure range up to about 0.15 mg/m^3 over 40 years".

A final remark (which was common in other authors) was: "The effect of smoking and presence of silicosis and their interaction on the lung cancer-RCS exposure response relationship remains un-

clear and further studies are required to evaluate the exact nature of the relationship".

The report by Morfeld (18), also commissioned by EUROSIL, summarised the epidemiological evidence of lung cancer-silica-silicosis association available up to date as the basis for the main purpose of the paper, which was devoted to providing RCS with a "Rationale for Classification According to CLP Regulation and within the Framework of the Globally Harmonised System (GHS) of Classifications and Labelling of Chemicals" (title of the paper).

The classification and Labelling of Chemicals (CLP) Regulation [Regulation (EC) No. 1272/2008] (7) implements in Europe the Globally Harmonised System developed under the auspices of the United Nations.

We report only the final conclusions: "The lung cancer risk is restricted to subjects who contracted silicosis. It has been accepted that minimising the silicosis risk will also minimize lung cancer risk due to RCS. This observation supports the suggested mode of action that RCS may produce cancer indirectly via inflammation. A potential direct genotoxicity can only be indicated at levels of RCS exposure far beyond the exposures necessary to cause inflammation. In conclusion, there is no requirement to classify RCS as a carcinogen if silicosis is used as the pivotal endpoint for classification".

Some actions undertaken within the EU

The Scientific Commission for the Occupational Exposure Levels (SCOEL) (23) published its recommendation some 5 years after the RCS IARC Classifications (SCOEL/SUM/94-final, 2003) stating that: "The main effect in humans of inhalation of respirable silica dust is silicosis. There is sufficient information to conclude that the relative risk of lung cancer is increased in persons with silicosis (and, apparently, not in employees without silicosis exposed to silica dust in quarries and in the ceramics industry). Therefore, preventing the onset of silicosis will also reduce the cancer risk. Since a clear threshold for silicosis development cannot be identified, any reduction of exposure will reduce the risk of silicosis. (…) It arises that an OEL should lie below 0.05 mg/m^3. …".

This opinion and the subsequent recommendations were shared by the British Health and Safety Executive (HSE) (9).

Based on this document the European Community accepted and supported, under its auspices, the proposal of an agreement between social partners (Employees and Employers) aimed at preparing guidelines for RCS prevention in occupational settings. At that time the EC did not repute it necessary to put RCS in the list of substances to be evaluated for carcinogenicity.

The Agreement on Worker's Health Protection Through the Good Handling and Use of Crystalline Silica and Products Containing it was published in 2006 (6).

The main objective of the agreement was to protect the health of workers exposed to RCS through the application of "Good practices", as specified in previous Directives. Protocols for environmental monitoring and worker health surveillance were annexed to the Document. Again, no indication was given as to the need for classifying RCS as a human carcinogen.

A further action was taken in 2008, when the Institute of Occupational Medicine of Edinburgh (IOM) and its partners were contracted by the European Commission to undertake a Socio-economic Health and Environmental analysis of proposed changes to the Carcinogen Directive (10). The first objective was to evaluate the impact of introducing a system for setting OELs based on objective risk criteria. RCS was included in the list of substances to be evaluated (Work Packages 6 and 8.1) also (we believe) because of the large number of subjects (3,200,000) presumed to be occupationally exposed to silica in the EU.

We are waiting for the final report.

The opinion of the Italian Society of Occupational Medicine and Industrial Hygiene (SIMLII)

More than 13 years have elapsed since the IARC Monograph (11) on silica was published.

During this period a substantial number of publications were made available on the question of silica-lung cancer association. In our opinion, little has changed concerning the still open issue of the carcinogenicity of silica *per se*, whereas the silicosis-lung cancer association now seems definitely confirmed. Many authors claim that there is a need for further investigations.

However, we think that it is unlikely that traditional epidemiology will in the future be able to provide a solid basis to solve the question, due to the fact that even the most sophisticated statistical procedures cannot balance the somewhat poor quality of the data, especially those regarding exposure assessment, and the difficulties in carrying out separate analysis for non-silicotics and "true silicotics".

A promising approach was suggested by Cocco ed al (5), in that they stated that "Future studies on lung cancer risk among workers exposed to silica-containing dust should consider measurements of ROS and TNF-alpha release by workplace dust samples as intermediate endpoints predicting lung cancer risk better than silica concentration, allowing to more effectively address preventive action".

This approach is innovative; but how can it be applied to data on exposures that occurred in the past?

We believe that in the present state of the art, attention should be focused on the following points:

- According to the current attitude of the EU on the question there is no need for labelling RCS with phrase H350i (ex R49-carcinogen by inhalation).

- Enforcing compliance with the current OELs by a stringent control in industrial settings is of primary importance. Further lowering of exposure limits is in agreement with the principle that minimizing the risk of silicosis will also minimize the risk of lung cancer. In fact SCOEL (23) suggested an OEL somewhat below 0.05 mg/m^3. The American conference of Governmental Industrial Hygienists (ACGIH) has already lowered its TLV to 0.025 mg/m^3. However, although even lower limits would obviously be more protective, the error associated with measurements (depending on the methods of air sampling and instrumental analysis) would be much higher. UNICHIM (26) estimated a ± 50% error when halving exposure limits. Anyway, the full application of "good practices" would carry the same importance.

- Implementing health surveillance should be included in future guidelines specific for silicosis risk. As an initial step we suggest that workers with even initial radiological signs of silicosis should by monitored over time by Spiral CT for early diagnosis of lung cancer (19).

At individual level it appears reasonable, for legal medicine purposes, that only lung cancer cases with unquestionable diagnosis of silicosis should be recognised as of occupational origin.

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