Seminario:
"Aggiornamenti sulla sorveglianza sanitaria degli esposti a silice"

Parma, 4 ottobre 2012

Silice e cancro: aspetti tossicologici e valutazione del rischio

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1. What is the evidence for a causal association between silica and cancer?

2. What does this evidence suggest in terms of human risk and exposure limits?

3. What are the practical & legal implications?

4. What recommendations can we reasonably gain?

5. Final remarks
Definitions

- **Silica** refers to silicon dioxide (SiO2), either in a crystalline or non-crystalline (amorphous) form.
- **Crystalline silica** may be found in various forms (polymorphism): 
  - alpha quartz
  - beta quartz
  - tridymite
  - cristobalite
  - keatite
  - coesite
  - stishovite
  - and moganite
- **Quartz** is so abundant that the term is often used in place of the general term crystalline silica.
- **Respirable crystalline silica (RCS)** is more appropriate for health risk assessment.

1. What is the evidence for a causal association between silica and cancer?

   - Epidemiological evidence
   - Experimental evidence
   - Mechanism of toxicity
Bradford Hill’s criteria of causation for an observed association

1. **Strength**: A strong association is more likely to have a causal component than is a weak association
2. **Consistency**: The same association is observed repeatedly under different conditions
3. **Specificity**: A causal factor influences specifically a particular outcome or population
4. **Temporality**: The causal factor must precede, not follow, the outcome it is assumed to affect
5. **Biological gradient**: A dose-response curve is observed, i.e. the outcome increases with increasing level/dose of exposure
6. **Plausibility**: The observed association is biologically plausible, i.e. it can be plausibly explained by substantive scientific evidence, based on the knowledge available
7. **Coherence**: A causal conclusion should not fundamentally contradict present substantive knowledge
8. **Experiment**: Causation is more likely if the association is based (also) on experimental evidence
9. **Analogy**: For analogous exposures and outcomes a similar effect has already been shown

“The Environment and disease: association or causation?”
Proceedings of the Royal Society of Medicine 1965; 58:295-300

Epidemiological studies on silica exposed workers (summary data)

- An increased risk of lung cancer was observed in several cohort and case-control studies from various countries, work settings and authors (SMR ranging 1.1 to 3.9 and OR ranging 1.5 to 3.9).
- RR from pooled- and meta-analyses ranged 1.70 to 3.27 for silicotics, 1.25 to 1.29 for silica-exposed workers and it was borderline or non significant for non silicotics, depending on smoking adjustment (0.96 to 1.2).
- In some studies a clear exposure-related effect was observed.
- Smoking and other confounders may have impacted the results of individual studies.

| Table 2 - Carcinogenicity studies of inhaled crystalline silica or quartz in rats |
|----------------------------------|----------------------------------|----------------------------------|
| Species, strain (sex)            | Dosing regimen                   | Incidence of tumours             |
| Duration                         | Animals/group at start            |                                  |
|                                  | Particle size; GSD*               |                                  |
| Rat, Fischer 344 (M, F) 24 months | 0.5 mg/m³ quartz (Miu-U-5)        | Lung epidermoid carcinomas       |
| (Dagel et al., 1986) (17)        | 6 hours/day, 5 days/week, 72 rats/sex | Male 0/42 (control), 1/47         |
|                                 | MMAAD, 1.7-2.5 μm; GSD, 1.9-2.1 | Female 0/48, 10/33               |
| Rat, Fischer 344 (F) 83 weeks    | 0.12 mg/m³ quartz (Miu-U-5)       | Lung tumours 0/54 (control), 18/60 |
| (Holland et al., 1983; 1986;    | 6 hours/day, 5 days/week, 62 rats | (11 adenocarcinomas, 3 squamous cell carcinomas, 6 adenomas) |
| Johnson et al., 1987) (38, 39, 44)| MMAAD, 2.24 μm; GSD, 1.75 |                                  |
| Rat, SPF Fischer 344 (M, F) 24 months | 0.1 mg/m³ crystalline silicon     | Lung tumours 0/100 (control M, F) |
| (Mohle et al., 1989, 1991,       | dioxide (876 crystallinity as quartz) | 7/20 (M, 12/50 (F)               |
| 1993) (56-58)                   | 6 hours/day, 5 days/week, 50 rats/sex | MMAAD, 1.5 μm; GSD, 1.8          |
| Rat, Wistar (F) 29 days          | 0.6 mg/m³ quartz (Miu-U-5)        | Lung tumours 0/85 (control), 37/82 (low dose), 43/82 (high dose) |
| (Sipioff et al., 1992) (73)      | 6 hours/day, 5 days/week, 90 rats | Multiple tumours/rat              |
|                                 | MMAAD, 1.8 μm; GSD, 2.0          |                                   |

*GSD, geometric standard deviation
*MMAAD, mass median aerodynamic diameter

(Guha et al., Med. Lav. 102:310-320)

| Table 3 - Carcinogenicity studies of intratracheally instilled silica in rats |
|----------------------------------|----------------------------------|----------------------------------|
| Species, strain (sex)            | Dosing regimen                   | Incidence of tumours             |
| Duration                         | Animals/group at start            |                                  |
|                                  | Particle size                    |                                  |
| Rat, Sprague Dawley Life span    | 0.7 mg quartz (Min-U-5)           | 0/40 (control), 6/36 (1 adenoma, 5 carcinomas) |
| (Holland et al., 1983) (38)      | Once a week, for 10 weeks 40 rats |                                 |
|                                 | MMAAD, 1.7 μm                    |                                  |
| Rat, Fischer 344 (M) 22 months   | 0.20 mg quartz (Min-U-5) once only | 1/75 (control), 30/75 (All adenocarcinomas) |
| (Groth et al., 1986) (34)        | 85 rats; MMAAD, < 5 μm             |                                  |
| Rat, F144/Ncr (M, F) 17-26 months| 0.32, 20 mg quartz                | M: 0/32 (control), 12 mg, 12/14 (Min-U-5) |
| (Saffo et al., 1990; 1992)       | Once only                        | F: 7/9 (HP-etched Min-U-5); 5/5 (F120, controls), 12 mg. |
|                                 | Unspecified number of rats       | 8/9 (Min-U-5); 8/9 (HP-etched Min-U-5); 20 mg, 0/3 (Min-U-5) |
|                                 | MMAAD, 0.5-2.0 μm                |                                  |
| Rat, Wistar Life span            | 0.5 mg one single or 15 weekly injections | adenoma, adenocarcinoma, benign cystic keratinizing squamous cell tumours, and other types of tumours in the lung |
| (Port et al., 1994) (61)         | of one of 3 types of quartz (DQ, 12, Min-U-5, F600) |                                  |
|                                 | Some rats received PVNO* to protect against silica |                                 |
|                                 | MMAAD: 2.5-5.0 μm; GSD: 1.7-2.1  | 37-56 cases/group; MMAAD not specified |

*PVNO, polyvinylpyrrolidone N-oxide
*MMAAD, mass median aerodynamic diameter
*Hydrogen fluoride
*Other types of tumours in the lung: fibrosarcoma, lymphosarcoma, mesothelioma or lung metastases from tumours at other sites (Ghura et al., Med. Lav. 102:310-320)
Carcinogenicity of RCS or quarz by inhalation/instillation in rats

*(summary data)*

- Treatment with crystalline silica increased the incidence of lung tumors in various strains of rats, in both males and females.
- In some studies a dose-related effect was observed.
- Tumours included adenomas, adenocarcinomas and squamous cell carcinomas

IARC classification of crystalline silica (quartz and cristobalite)

- 1987, Group 2A *(probably carcinogenic to humans)*
- 1997, Group 1 *(carcinogenic to humans)*
- 2010, Group 1 confirmed by a separate Working Group

“The Working Group reaffirmed the carcinogenicity of crystalline silica dust as Group 1. An increased risk of lung cancer was observed across various industries and processes.”

<table>
<thead>
<tr>
<th>Group 1 agent</th>
<th>Tumour sites</th>
<th>Established mechanistic events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silica dust, crystalline quartz or cristobalite</td>
<td>Lung</td>
<td>- Impaired particle clearance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Macrophage activation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Persistent inflammation</td>
</tr>
</tbody>
</table>

*(Straif K et al., *Lancet Oncol.*, 2009, 10(5):453-4)*
Proposed mechanisms for silica carcinogenicity

Three different, not necessarily alternative mechanisms (including genotoxic and non genotoxic ones) have been proposed by IARC for silica carcinogenicity:

- 1. phagocytosis, impaired clearance and macrophage activation or apoptosis (epigenetic mechanism)
- 2. inflammation and extracellular formation of reactive oxygen species (ROS) leading to DNA damage and cell proliferation (“mixed” mechanism)
- 3. intracellular ROS formation and direct DNA damage (genotoxic mechanism)

(IARC Monographs n. 42/1997 and 68/1997)

Mechanism of damage of crystalline silica to the lung

- Phagocytosis of crystalline silica leads to active swelling of phagosomes, and release of their contents into the cytosolic compartment of macrophages.
- Activation of the NALP3 inflammasome by a silica crystal after initial priming by a lipopolysaccharide also necessitates generation of ROS
- The resulting active enzyme inflammasome activates the potent proinflammatory molecules such as IL-1β and IL-18 leading to inflammation

ROS=reactive oxygen species. ASC=apoptosis-associated speck-like protein containing a caspase recruitment domain. NF-κB=nuclear factor-κB. IL=interleukin

(Lancet, 2012)
### Classification of crystalline silica by other Agencies/Bodies

- **ACGIH** (TLV® & BEI®, 2009): **cncr (plmn)** (*carcinogenic for the lung*)

- **NIOSH** (DHHS Publication No. 2002–129): “*potential human carcinogen*”, and “…epidemiologic studies indicate that workers exposed to respirable crystalline silica have an increased risk of developing lung cancer…”

- **American Thoracic Society** (ATS, 1997) official statement: “the available data support the conclusion that **silicosis produces increased risk for bronchogenic carcinoma**.” However, the ATS noted that **less information was available for lung cancer risks** …for silica-exposed workers who did not have silicosis and concluded that it was “less clear whether silica exposure was associated with lung cancer in the absence of silicosis.”

- **SCOEL** (2003)
  
  “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…).
  
  - 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/m3.**”

  (an OEL of 0.05 mg/m3 will reduce ILO 1/1 to less than 5%)

  (SCOEL SUM Doc 94-final, June 2003)
SCOEL strategy for classification of carcinogenic substances

- **Group A** – non-threshold genotoxic carcinogens
  A linear non-threshold (LNT) model of extrapolation of test results from animals (high doses) to humans (low doses) is used; e.g. 1,3-butadiene and vinyl chloride

- **Group B** – genotoxic carcinogens
  The existing data are not sufficient to apply the LNT model; e.g. acrylonitrile, benzene, naphthalene and wood dusts.

- **Group C** – weak genotoxic carcinogens
  A practical threshold can be set based on existing data; e.g. formaldehyde, vinyl acetate, nitrobenzene, pyridine, *crystalline silica* and lead.

- **Group D** – non-genotoxic and non DNA-reactive carcinogens
  A threshold can be set based on NOAEL; e.g. carbon tetrachloride and chloroform.

Note: Health-based OELs are derived by SCOEL only for carcinogens "C" and "D", whereas for carcinogens "A" and "B" other factors are considered (socio-economic, technical, political, etc.).

(Bolt and Huici-Montagud, 2008; SCOEL, 2010)
Italian Society of Occupational Medicine and Industrial Hygiene (SIMLII)

*(document in progress open to the public since April 2012)*

Tentative conclusions:

- Agreement with EU position **not to classify** RCS as a human carcinogen
- Consideration of the 1997 IARC reaffirmed (2009) conclusion for a **sufficient evidence** that crystalline silica dust is a human carcinogen
- Considering the limits recommended by SCOEL (OEL = 0.05 mg/m³) and ACGIH (TWA-TLV = 0.025 mg/m³), lower values might be **difficult to assess** based on current analytical techniques
- A stronger (control of) **compliance with the OEL in industrial settings** is necessary to prevent both silicosis and lung cancer
- **Cessation of cigarette smoking** and **inclusion in oncologic prevention programmes** should be strongly recommended to workers with initial radiological signs of silicosis

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**Silica exposure and lung cancer**

an assessment based on Bradford Hill’s criteria for causation

*the overall compliance “of each criterion, according to the author’s perception”, is indicated on a scale from +/- to +++*
Bradford Hill’s criteria of *causation* for an observed *association*

1. Strength
2. Consistency
3. Specificity
4. Temporality
5. Biological gradient
6. Plausibility
7. Coherence
8. Experiment
9. Analogy

“The Environment and disease: association or causation?”
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1. **Strength (+)**

   A strong association is more likely to have a causal component than is a weak association

   - RR is *high for silicotics* (1.70 to 3.27), *low for silica-exposed* workers with and without silicosis together) (1.25 to 1.29), and *statistically non significant* for workers without silicosis.

   This provide substantial evidence that the association is indeed causal for silicosis but not for silica exposure alone.
2. Consistency (+++)

The same association is observed repeatedly under different conditions, times, populations or settings

- Studies have reported an association between silica exposure and lung cancer since the 80's to recent times, from various countries, different industrial settings and by different investigators.
- For silica without silicosis the evidence so far is missing (studies since 2004 only).

Again this supports the belief that this relationship is causal for silicosis, not for silica per se.

3. Specificity (+/-)

A causal factor influences specifically a particular outcome (disease) or population

- Lung cancer is a widespread disease totalling over 16% of all cancers and over 18% of all deaths from cancer in man worldwide.
- Besides, there are many causes of lung cancer.

This criterion is not helpful in coming to a decision.
4. Temporality (+++)

The causal factor must precede, not follow, the outcome it is assumed to affect

- This is a very important criterion in some cases, because the "cause" must precede the outcome and the latent period between first exposure and the first outcome must be plausible.

This is true but not very critical in the present case. (Since lung cancer risk was found to increase with the duration of exposure and latency it would be helpful to compare latency for the two diseases in the same study, but this is difficult, particularly for silicosis)

5. Biological gradient (++)

A dose-response curve is observed, i.e. the outcome increases with increasing level/dose of exposure

- A dose-response relationship between silica exposure and lung cancer has been suggested in various studies which, however, ignored the presence of silicosis or not.
- No evidence of a biological gradient is available in non-silicotics exposed to silica so far.

This criterion, therefore, although potentially very important does not support per se causation.
6. Plausibility (+)
The observed association is biologically plausible, i.e. it can be explained by substantive scientific evidence, based on the best knowledge available

- The mechanism of action of silica on the lung has been extensively investigated and it is now reasonably well established for silicosis.
- No established mechanism, however, is available for silica carcinogenicity: both genotoxic and epigenetic mechanisms have been proposed.

Hence one cannot attach too much weight to this criterion

7. Experimental evidence (++)
Causation is more likely if the association is based (also) on experimental evidence

- Crystalline silica caused clear carcinogenic effects in the lung of rats (not mice or hamsters) at levels of exposure as low as 0.1 mg/m³.
- Effects were clearly dose-related.

These observations provide support to a causal relationship, although extrapolation of animal data to humans is difficult.
8. Analogy (+/-)
For analogous exposures and outcomes a similar effect has already been shown

- **No related exposures or outcomes** have been clearly documented.
- Reports of increased relative risks for **other types of cancer** have not been confirmed or consistent.
- Asbestos-dependent lung cancer might indicate an analogy, although mechanism of action, physico-chemistry and clinical features are quite different.

So, this criterion is not very useful.

9. Coherence (+)
A causal conclusion should not fundamentally contradict present substantive knowledge

- If one consider the overall coherence of all the evidence (epidemiological, experimental, mechanistic) one would agree that a causal relationship between silica exposure and lung cancer is **largely justified in silicotics, much less so in non-silicotics.**
2. What does this evidence suggest in terms of human risk assessment and exposure limits?

Risk assessment of occupational exposure to crystalline silica: critical factors

- Composition of dust (% of crystalline components)
- Conditions of exposure (including workload, coexposure, etc.)
- Duration of exposure (daily, weekly, lifetime)
- Preventive measures (ventilation, PPE)
- Individual susceptibility (chronic respiratory diseases)
- Level/duration of exposure (cumulative exposure to respirable fraction)
OCCUPATIONAL EXPOSURE LIMIT VALUES FOR CARCINOGENS BY SCOEL

- Occupational Exposure Limit Values for carcinogenic substances by the European Scientific Committee on Occupational Exposure Limits (SCOEL) depend on the type and mechanism of their carcinogenic effect, mainly on whether or not the substance is genotoxic but also the type and degree of genotoxicity.

**OEL for crystalline silica has been set following classification as group C:** a health-based OEL for a weaky genotoxic (threshold ?) carcinogen

<table>
<thead>
<tr>
<th>Agency (year)</th>
<th>Exp. limit</th>
<th>Material</th>
<th>Exposure condition</th>
<th>value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACGIH (2009)</td>
<td>TWA-TLV</td>
<td>crystalline silica</td>
<td>TWA, 8 hr/day, 40 hr/week</td>
<td>0.025 mg/m³</td>
</tr>
<tr>
<td>NIOSH (2009)</td>
<td>REL</td>
<td>respirable crystalline silica</td>
<td>TWA-EL, 10 hr/day, 40 hr/week</td>
<td>0.05 mg/m³</td>
</tr>
<tr>
<td>OSHA</td>
<td>PEL</td>
<td>respirable dust containing quartz</td>
<td>TWA-EL, 10 hr/day, 40 hr/week</td>
<td>0.1 to 5 mg/m³</td>
</tr>
<tr>
<td>SCOEL</td>
<td>OEL</td>
<td>crystalline silica</td>
<td>TWA, 8 hr/day, 40 hr/week</td>
<td>0.05 mg/m³</td>
</tr>
</tbody>
</table>

* depending on 100 to 90 % crystalline silica present in the sample, respectively.
OCCUPATIONAL EXPOSURE LIMITS (OELs) in the E.U.

• Indicative Occupational Exposure Limit Values (IOELVs)
  – Health-based, non-binding values, derived from the most recent scientific data.
  – They set threshold levels of exposure below which, in general, no detrimental effects are expected for any given substance over a working lifetime.
  – They constitute European objectives to assist employers in determining and assessing risks

• Binding Occupational Exposure Limit Values (BOELVs)
  – They take into account also socio-economic and technical feasibility factors and policy considerations are of major importance.
  – For any chemical with a BOELV, Member States must establish a corresponding national binding OEL value which can be stricter, but cannot exceed the Community limit value.
  – BOELVs are published in the European Parliament Directives.

3. What are the practical & legal implications?

• Risk management
  – Regulation (CLP)
  – Limit values
  – Control and sanctions

• Health surveillance
  – Classification of exposed subjects
  – Health monitoring
  – Health promotion

• Compensation/legal action
4. What recommendations can be reasonably gained?

- **For scientists:**
  Stronger interaction among epidemiologists, toxicologists and exposure scientists in future studies (*individual susceptibility, coexposure, confoundings*, etc.)

- **For regulators:**
  Rational decision making based on both: a rigorous scientific approach and other considerations (*technical, socio-economic, political*, etc.)

- **For occupational physicians:**
  Best OH practice and compliance with ethical principles (*ICOH Code of Ethics*)

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Final remarks

- Current evidence supports a *causal relationship* between silica exposure and lung cancer, although epidemiological evidence is limited to workers with silicosis.

- A *carcinogenic effect of RCS per se*, *i.e.* in the absence of silicosis, has yet to be demonstrated but cannot be excluded based on experimental and mechanistic data.

- There is a lack of evidence of a *threshold dose* for silicosis and also for carcinogenicity, if any, due to uncertainty on the possible mechanism.

- So, one has to assume that *lower levels of exposure may decrease both risks* and, therefore, *exposure limit values* should be kept as low as practically, technically, and politically achievable.