Prevention, ethics and science: lessons from Lorenzo Tomatis

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Summary. This paper is dedicated to Lorenzo Tomatis, former director of the International Agency for Research on Cancer (IARC), promoter of prevention principles with a precautionary approach, supported by an important scientific foundation. He has recommended an appropriate consideration of both "false negatives" and "false positives" errors in the evaluation of epidemiological and experimental data on toxicological and carcinogenic risk. The current rules for IARC Monographs preparation include both a full transparency of the data used and of the possible conflicts of interest of the experts involved. Tomatis has also underlined that "Dismissing animal carcinogenicity findings would lead to human cases as the only means of demonstrating carcinogenicity of environmental agents. This is an unacceptable public health policy". The main role of experimental studies is presently included in both the new preamble of IARC Monographs and the method adopted for the World Health Organization Air Quality Guidelines for low-dose carcinogenic risk assessment.

Key words: cancer risk, prevention, ethical consideration, precautionary principle.

Riassunto *(Prevenzione, etica e scienza: la lezione di Lorenzo Tomatis)*. Questo lavoro è dedicato a Lorenzo Tomatis, già direttore della International Agency for Research on Cancer (IARC), e promotore di principi di prevenzione con un approccio cautelativo basato su criteri scientifici. Tomatis ha raccomandato un'adeguata considerazione congiunta della possibilità sia di "falsi positivi che "falsi negativi" nella valutazione di dati epidemiologici e sperimentali sul rischio tossicologico e cancerogeno. Le correnti procedure per la predisposizione delle monografie della IARC includono una piena trasparenza per i dati usati e per possibili conflitti di interesse per gli esperti coinvolti. Tomatis ha anche sottolineato che "qualora si omettesse la considerazione degli effetti cancerogeni su animali, la casistica dei tumori in soggetti umani costituirebbe l'unico criterio disponibile per dimostrare la cancerogenicità di agenti ambientali". Un ruolo fondamentale degli studi su animali è presente nel recente "preambolo" delle Monografie IARC e nel metodo impiegato nelle Linee Guida per la Qualità dell'Aria dell'Organizzazione Mondiale della Sanità per la valutazione del rischio a basse dosi.

Parole chiave: rischio cancerogeno, prevenzione, considerazioni etiche, principio di precauzione.

"In the absence of absolute certainty, rarely if ever reached in biology, it is essential to adopt an attitude of responsible caution, in line with the principles of primary prevention, the only one that may prevent unlimited experimentation on the entire human species"
L. Tomatis, 2002

INTRODUCTION

Since many years, Lorenzo Tomatis has stressed the fundamental necessity of prevention-aimed studies and strategies in public health research and management. As is well known, the Monographs of the International Agency on the Research on Cancer (IARC), that Lorenzo Tomatis has planned, created and directed, have represented and represent a fundamental and exhaustive information source for prevention strategies, providing important scientific and ethical criteria in this field. It is worthwhile noticing that the existing rules for IARC Monographs preparation include: "The critical review of pertinent peer-reviewed scientific literature (sections 1-4) considers all published articles, plus articles accepted for publication. Reports and documents from national and international government agencies considered if they are publicly available. Consensus reports in the published literature are also considered, subjected to some critical review as other articles, including the consideration of the composition and balance of the panel that produced the consensus. Research not publicly available, including articles in preparation, is not considered" [1]. Moreover, the IARC procedures concerning the declaration of interests by participants at IARC Monographs meetings in-

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clude the need of declaring "any interest that could constitute a real, potential or apparent conflict of interest, with respect to his/her involvement in the meeting or work". The conflict of interest means "the expert or his/her partner, or the administrative unit with which the expert has an employment relationship, has a financial or other interest that could unduly influence the expert's position with respect to the subject-matter being considered". An "apparent conflict of interest" concerns a condition of a non necessary influence on the expert, but also of the possibility of an "expert's objectivity being questioned by others" [2]. The availability to the scientific community and to risk managers of the whole information on which health evaluations are based, together with the adopted evaluation criteria, and the need of declaration of any possible conflict of interest of experts involved in this activity reflect a scientific and ethical principle (full transparency and full independent judgement) that Tomatis has repeatedly asserted.

PREVENTION AND PRECAUTIONARY APPROACH

Another argument pointed out by Lorenzo is the tendency, in risk evaluation studies, to avoid "false positives", with scarce attention to the possibility of "false negatives". He has observed that, from the public health point of view, the production of "false negatives" is an error that may be more serious than the production of "false positives" [3].

It is worthwhile noticing that the problem of "false negatives" has also been recently underlined in a paper published by the responsible of the IARC carcinogen identification and evaluation "A stress on avoiding false positives generally implies an abundance of false negatives" [4]. Moreover, in a paper on the precautionary principle, recently published by a researcher from the World Health Organization (WHO), it is reported that "For example, epidemiological inquiry following the Popperian scheme of hypothesis generation and testing typically has high specificity and low sensitivity – that is, false positives are penalised more heavily than false negatives" [5].

It may be useful to briefly remind here some classical statistical criteria concerning "false positives" and "false negatives", which clarify that the above considerations have a solid scientific base. As is known, the "false positive error", also named "Type I error" or "α error" , is the error of rejecting the "null hypothesis (Ho)" when it is actually true: in simple words, this is the error of accepting the hypothesis of interest (Hi) when the results are attributable to chance (Ho hypothesis). The usual significance parameter "p" (*e.g.*, $p < 5\%$) represents the probability of Ho. However, it should be considered that the standard significance parameters (*e.g.*, $p < 5\%$ or $p < 1\%$, or other) do not constitute a "wall" qualitatively dividing "significant" or not "significant" (or yes/not) results. The Ho probability is a quantitative continuous parameter to be examined as such: *e.g.*, if the obtained significance level is 6% instead than 5%, the difference is obviously very small, and this should not be neglected; in both cases the probability of "false positives" is low, and the difference is practically negligible. The "false negative error", also named "Type II error" or "β error", is the error of failing to reject the null hypothesis (Ho) when the alternative hypothesis of interest (Hi) is true; in simple words, it is the error of failing to consider a difference when it is true, attributing the obtained result to chance. The estimation of the Type II or β error is more complex than the one of Type I error, and implies a specific definition of the hypothesis of interest (Hi) and the consideration of background or control levels of the examined parameter. The "statistical power" of an experiment or an epidemiological observation is the probability of the rejection of a false negative. The statistical power obviously increases with the increase of the size of the adopted samples and of the difference to be tested. The definition of the experimental designs of epidemiological or animal studies requires to select the size of the samples suitable to obtain a statistical power appropriate for the verification of the hypothesis of interest. For instance, with a very rough example, if the hypothesis (Hi) of a risk increase of 0.1% (1/1000) in the exposed group has to be tested, compared with a control response is for instance of 0%, and if sample sizes of 100 subjects are adopted for the exposed and control groups, it is *a priori* evident that the probability of obtaining a null result (null incidence in the exposed group and no difference among the exposed group and the control) is remarkably high (more than 90%), even if Hi is true. Evidently, in this case the adopted sample sizes are too small for testing the assumed Hi hypothesis and the statistical power is inappropriate (*i.e.*, in other words, it is not possible to see bacteria only with a common lens, a good microscope is necessary). In the case of a non null control (or spontaneous rate) incidence, the appropriate sample (or group) sizes increase with the increase of the control incidence (or spontaneous rate) for testing the same excess rate. For instance, it has been estimated that the minimum group sizes for reasonably ensuring a significance value $p \leq 5\%$ in the case of an excess rate of 10% over spontaneous rates of 1%, 10% and 20%, should respectively be 121 (close to the usual size adopted in experimental studies), 289 and 423 [6]. This clearly shows the difficulty of identifying, with a $p \leq 5\%$ significant level, incidence increases lower than 10% over a non null control (or non null spontaneous rate) when the group sizes are limited. Only when the background incidences of the studied adverse effect are extremely low and when its cause is substantially a single one (*i.e.*, alternative causes are very improbable), these problems may be remarkably reduced. The classical examples are the cases of haemangiosarcoma of the liver induced by vinyl chloride monomer and of mesothelioma in-

duced by the asbestos. These tumours are extremely rare in the general or occupational populations not exposed to these agents, so that very few cases observed in numerically limited groups (*e.g.*, 100 exposed workers), are very unlikely attributable to the background rate and even a single case may suggest a possible risk ("sentinel event"). As a consequence, as is well known, asbestos and vinyl chloride are currently recognized as "occupational carcinogens", while this does not happen for other important categories of cancer attributable to several different agents (many of them making part of occupational exposure) and not only to a single one, and characterized by a not low background risk (*e.g.*, lung cancer).

The above considerations suggest the need of an appropriate caution level in risk evaluation: "Scientists describe the potential implications and limitations of their data, and risk management officials should be prepared to act on this knowledge, giving appropriate consideration to findings that are plausible but not fully established (…). Precaution means that risk management officials are prepared to act on less than sufficient evidences when warranted. The scientific evaluation serves to indicate when precaution may be appropriate in risk management" [4]. Lastly, "epidemiology generally cannot rule out a cancer hazard until more than 20 years of exposure have occurred, and it cannot rule out 1 in 10 000 risk unless tens of thousands of people have been exposed" [4]. It is worthwhile noticing that the 1 in 10 000 risk is the higher risk level among the ones considered as precautionary reference for cancer prevention management by the WHO [7-9], the US Environmental Protection Agency (USEPA) [10] and other institutions. In practice, these precautionary criteria for low dose carcinogenic risk assessment and management (assumption of linear dose-response trend for low doses, consideration of its confidence limits, reference to exposures corresponding to risk levels of 10^{-4}, 10^{-5} and 10^{-6}) deal with risk levels that *a priori* are expected to be not epidemiologically verifiable (as shown by the above statistical power considerations).

The results of the epidemiological study "15-Country collaborative study of cancer risk among radiation workers: estimates of radiation-related cancer risk" [11-13], coordinated by the IARC, are of main interest for this discussion. This study (the largest one on nuclear workers ever carried out) is based on the analysis of 407 391 nuclear industry workers whose external exposure monitoring data were available, and therefore is characterized by a very high statistical power. It has indicated a low but significant excess cancer risk, even at the low doses and dose rates typically received by the considered nuclear workers. The reported average dose is 19.4 mGray and a 1-2% of the observed cancer (other than leukaemia) deaths were estimated to be attributable to radiation exposure. The results of this study are coherent with risk estimations based on the low-dose linear models for carcinogenic risk assessment, and may provide an important reference for the evaluation of the radiation risk in other contexts, as, in particular, in the case of the Chernobyl accident affected populations, for which another IARC coordinated study has estimated the cancer burden [14]. A remarkably high number of estimated radiation-attributable cases, for all cancers other than leukaemia, thyroid and non-melanoma skin cancers, however distributed on very large populations, was predicted making use of validated mathematical models (the resulting absolute risk levels are low and mostly very low and so happens for the radiation attributable fraction) except for the people resident in the most contaminated areas or for the occupationally exposed people at radiation high levels – the "liquidators". As a consequence, an epidemiological verification of these risks will be very difficult or practically impossible, in particular in the case of "geographic" studies. However, the above mentioned "15-country study of cancer risk among radiation workers" clearly indicates that in the Chernobyl accident remarkably affected areas, and in particular the ones with exposure levels in the order of that of nuclear industry workers a non negligible risk may be expected to exist, even if extremely difficult to be epidemiologically verified [15].

Tomatis has repeatedly asserted the importance of animal studies in cancer risk evaluations: "Dismissing animal carcinogenicity findings would lead to human cases as the only means of demonstrating carcinogenicity of environmental agents. This is an unacceptable public health policy" [16] and "The experimental approach to carcinogenicity can ascertain and predict potential cancer risk to humans in time for primary prevention to be successful" [17]. This is immediately evident if the time period required by an usual experimental carcinogenic study on rodents, typically lasting two years, is compared with the time needed for the epidemiological study to be planned, carried out and completed. In the case of a new carcinogenic agent introduced in the environment for the first time, a period of two decades or more could be necessary for obtaining a result (exposure period, latency of the effect after the exposure, data collection and analysis, etc.).

The principle of giving particular attention to experimental studies has been sometimes criticized, while, as stressed by Tomatis, it remains a main information source for prevention, recognized by main scientific institutions: "Our conclusions agree with the IARC, the National Toxicology Program and other respected scientific organizations: in the absence of human data, animal studies are the most definitive for assessing human cancer risk. Animal data should not be ignored, and precautions should be taken to lessen human exposures" and, also: "Animal data on the carcinogenicity of a variety of chemicals have preceded as well as predicted later epidemiological observations in humans" and "Strong evidence exists that experimental results can be extrapolated qualitatively the human subjects"

[16]. The animal to humans extrapolation of non-carcinogenic adverse effects is a common practise in the quantitative toxicity assessments (*e.g.*, acute and chronic toxicity data, and toxicity classification, also in EU usual procedures). Since a long time, the US EPA makes use the animal data more often than epidemiological data, for both non-carcinogenic and carcinogenic quantitative risk assessment (*e.g.*, US EPA IRIS file, Internet available).

The WHO *Air quality guidelines* [7, 9] present the carcinogenic "unit risks" (cancer risk estimates for a lifetime inhalation exposure to 1 $\mu g/m^3$ air concentration) for 12 main agents (single agents or families of agents). Among them, arsenic, benzene, vinyl chloride, asbestos, and radon are single agents classified in the Group 1 by the IARC ("sufficient evidence of carcinogenicity in humans", "carcinogenic to humans") with also "sufficient evidence in experimental animals", except for arsenic for which the evidence is "limited". Moreover, the IARC in its "Overall evaluation" (Monographs final conclusions), also classifies in the Group 1 (carcinogenic to humans) the chromium (VI) (hexavalent) [18], the nickel compounds [18] and various occupational exposures to polycyclic aromatic hydrocarbons, (during coal gasification, coke production, coal-tar distillation, chimney sweep, paving and roofing with coal-tar pitch) [19]. For these agents, a sufficient carcinogenicity evidence is also reported in experimental animals for exposures equivalent or in some way comparable to the human ones classified as carcinogenic. Other considered agents, characterized by a lower carcinogenicity evidence level, are: acrylonitrile (presently, classified in IARC Group 2B, "inadequate evidence in humans", "sufficient in experimental animals", but originally classified in Group 2A, "limited evidence in humans", "sufficient in experimental animals") (reported in this latter form in the WHO document), butadiene (IARC Group 2A, "limited evidence in humans", "sufficient in experimental animals"), the refractory ceramic fibres (IARC 2B, "sufficient evidence for carcinogenicity in experimental animals" and "no data were available on the carcinogenicity of ceramic fibres in humans) [20] and, lastly, trichloroethylene (IARC Group 2A, "limited evidence in humans", "sufficient in experimental animals) [21].

For all these 12 agents, the WHO underlines that no safe level may be recommended (absence of effect threshold), and only presents the corresponding "unit risk", together with the reference lifetime exposure levels associated to extremely low risk levels (air concentrations associated with 10^{-4}, 10^{-5} and 10^{-6} estimated risks). For butadiene, the "unit risk" has not been directly estimated by the WHO, which however reports the ones of the USEPA (USEPA IRIS file on line) and of the National Institute of Public Health and Environmental Protection of the Netherlands [22]. Lastly, it is important to observe that for refractory ceramic fibres (IARC Group 2B), the WHO presents an "unit risk" based on animal data, in the absence of human data.

It is worthwhile noticing that in this carcinogenic risk evaluation and assessment, the WHO has adopted principles in agreement with criteria underlined by Tomatis:

- agents not only classified in the IARC Group 1 are taken into account, but also agents classified in the Groups 2A and 2B have been conservatively considered. Therefore, an important weight has been given to experimental animal data and the "sufficient carcinogenic evidence" in humans has not been assumed as a necessary condition for risk assessment;
- the experimental animal studies have led to results substantially coherent with the ones of epidemiological studies;
- for the refractory ceramic fibres (IARC 2B, "sufficient evidence for carcinogenicity in experimental animals", "no data were available on the carcinogenicity of ceramic fibres in humans") the quantitative risk assessment has been based on experimental animal data;
- a no-threshold low-dose linear dose-response trend has been adopted for carcinogenic risk assessment, proposing, instead of guideline values (*i.e.*, quantitative limits), the reference to exposure levels for which the risk is extremely low, consenting to risk managers to select the risk level that they consider more appropriate. As above mentioned, these risk levels are practically not epidemiologically verifiable, because too small. Similar criteria are adopted by various Agencies (*e.g.*, USEPA, US FDA and by some European national institutions).

A last consideration is suggested by the analysis of the WHO document. The large majority of epidemiological studies leading to Group 1 classification of carcinogenicity, mostly published two or three decades ago, were dealing with exposure conditions, particularly in the occupational environment, existing many years before the onset of observed cancers. The prevention efficiency in that period was limited, because the information on cancer causes and risks was also limited. Recently, prevention strategies have been improved: the task for the future should be, whenever possible, to not observe cases of preventable cancers in the general and occupational populations. This also means, whenever possible, to eliminate or appropriately reduce human exposures possibly leading to "sufficient evidence of carcinogenicity in humans" (Group 1), or even to a less evident but reasonably expected risk for humans. For this, an improved production of animals studies, based on methodological criteria also consenting a suitable extrapolation for animals to humans, is necessary. Presently this seems possible: "In the absence of adequate data on humans, it is biologically plausible and prudent to regard agents and mixtures for which there is sufficient evidence of carcinogenicity in experimental animals as they presented a carcinogenic risk to humans" [23]. The Preamble of IARC Monographs (presenting the criteria for Monographs production) has recently been revised and new crite-

ria have been recently added. Among them, the use of "Mechanistic and other relevant data" (new title) that include toxicokinetic data, data on mechanisms of carcinogenicity, susceptibility data, as well as data on other adverse effects, focused on confirming distribution or biological effects at sites of tumour development. Moreover, another important added criterion needs to be underlined: "An agent may be classified as *possibly carcinogenic* (Group 2B) solely on the basis of strong evidence from mechanistic and other relevant data". It is worthwhile noticing that the IARC Advisory Groups recommended that both sexes of a single species in a GLP experimental study can also provide *sufficient evidence*. The new principles adopted in the recent Preamble [24] extend the classification rules towards a more precautionary address.

CONCLUSION

In conclusion, the principles often underlined by Tomatis for cancer prevention have an important foundation, both scientific and ethical, recognized and confirmed by many important institutions.

The subtitle of a recent paper on these topics is "Better health, better environment, better science: better use of the precautionary principle" [5]. The lessons from Lorenzo Tomatis remain a fundamental guidance for the future, to be taken into account and not neglected.

This article is dedicated to an outstanding scientific leader, promoter of basic ethical principles and, last but not least, our teacher, and our dear friend.

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