Commentary to "Mortality from Bladder Cancer in Dyestuff Workers Exposed to Aromatic Amines: A 73-Year Follow-Up" by C. Ciocan et al.

Ciocan et al. [1] describe an outbreak of bladder cancer among workers exposed to high levels of carcinogenic aromatic amines in a dyestuff factory in the province of Turin (Northern Italy). Findings are striking: during a 70-year follow up, 60 deaths from bladder cancer occurred in the cohort vs. 4.0 expected.

Not unusually for papers published in *La Medicina del Lavoro*, the name of the factory is not mentioned, which precludes an overall contextualization of the shameful episode in its geographical, historical, and social circumstances. However, my guess is that it was the IPCA (Industria Piemontese Coloranti Anilina) factory in Cirié, a town on the outskirts of Turin. In 1978, IPCA made history, when its managers were sentenced to jail for manslaughter in the first criminal court trial for occupational cancer ever taking place in Italy.

The working environment and conditions could hardly have been worse at IPCA that was a major player in the economy of the area. As reported by Ciocan et al., between 1946 and 1970 almost 600 men worked for at least one year at IPCA, while Cirié then had a population slightly above 10,000 inhabitants. Events and the trial had a great emotional impact on the population. Nowadays, one of Cirié's squares is dedicated to the IPCA victims and a street is named after Gino Franza and Albino Stella, the two IPCA workers who brought the bladder cancer deaths to the attention of the workers' union and subsequently of the judicial authority. Documents regarding the factory and the trial have been collected in a huge repository located in what is left of IPCA premises. I recommend Ciocan et al. to forward a reprint of their paper to the Mayor of Cirié for inclusion in the IPCA archive.

Given the relevance of the episode in the history of the area, a more precise measure of the impact IPCA had on the workers' health would be desirable. In Ciocan et al.' study, causes of death were not validated and bladder cancer morbidity was ignored. According to local witnesses, the actual number of victims exceeded the figure reported by Ciocan et al. An a priori count of bladder cancer prevalence in those days would be unfeasible. Ciocan et al. do not clarify whether the figure of 60 victims includes those identified through (death) certificates attributing death to conditions other than bladder cancer and mentioning bladder cancer among "other significant conditions contributing to the death". The article appears not to consider those certificates: would it be possible for the authors to count them and add the number of IPCA workers dying with bladder cancer? This would be an improved approximation to the actual number of IPCA victims.

> **Benedetto Terracini,** University of Turin (retired)

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Reply to The Commentary to "Mortality from Bladder Cancer in Dyestuff Workers Exposed to Aromatic Amines: A 73-Year Follow-Up" by C. Ciocan et al" by B. Terracini

The comments by B. Terracini to our paper "Mortality from bladder cancer in dyestuff workers exposed to aromatic amines: a 73-year follow-up" by Ciocan et al. [1] give us the opportunity to clarify some methodological aspects of our study.

We have not disclosed the identity of the industries that we have investigated in current or past cohort studies. The data, methodology, and findings from our investigations are being presented for the goal of demonstrating to the scientific community the impacts of one or more exposures on human health. We therefore took the same approach with this particular industry that had previously been the focus of multiple prior publications [2-4], all of which were follow-ups of the same cohort after various latencies and documented the effects of aromatic amine exposure on health.

We agree that the severe effects of that specific exposure provide proof of unacceptable working conditions. Our updated results add further scientific evidence to this conclusion. Finding additional bladder cancer deaths after 73 year of follow up confirms the results from previous analyses with excess risk of bladder cancer persisting several decades after stopping exposure, thus providing additional information on the carcinogenesis process following occupational exposure to aromatic amines.

The expected number of events, specifically deaths from bladder cancer, was calculated relying on death certificates. The observed number of deaths must result from the same source in order to be comparable and to estimate risk. The Italian death certification validity is recognized as robust even for a cause like COVID-19, for which death for and with the disease is a key issue [5]. Still, some mis-certification is possible in observed and expected figures, whose impact on risk estimates and their pattern over time is however likely to be limited.

Furthermore, the main goal of our research was not to determine the total number of incident cases within the cohort but rather to compare the new results to those of earlier analyses of the same cohort (also based only on mortality data) in order to understand the trend of the bladder cancer risk decades after the cessation of exposure.

About incident cases of bladder cancer, screening programs applied to workers that undergo health surveillance for preventive purposes do not apply to the general population. Initial cases that do not lead to overt disease or death from bladder cancer would be identified more frequently in the working population than in the general population. Members of this cohort did not have their urine cytology and health monitored while they were employed; rather, they entered our Institute's follow-up program after retirement.

We will be pleased to provide a copy of all of our publications on the matter to the mayor of the concerned municipality.

Catalina Ciocan, Alessandro Godono, Enrico Pira, Nicolò Franco

Department of Public Health and Pediatric Sciences, University of Turin, Turin, Italy

Carlo La Vecchia

Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy

Eva Negri

Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

Paolo Boffetta

Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy Stony Brook Cancer Center, Stony Brook University, Stony Brook, NY USA

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