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Review Article

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Toxic Encephalopathy After Dioxin Effects Preceding Clinical and Lethal Breast Cancer or Tumours of Secretory Organs as Pertinent Hazard Following Lacking Prevention?

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In cancer research aimed at the identification of causal associations between environmental and/or occupational unprevented exposure to dioxins as risk factors for cancer growth respectively promoting its progression as a result of exposure in occupational situations instigated growing attention to relevant contributing conditions as mandatory for ongoing efforts to intervene.

The inclusion of central nervous regulatory functions in causal connection after initiating carcinogenic factors by focussing on mixed attributive exposures with view to accompanied neurotoxic damage by failure of naturally competent resistance and their repair mechanisms deserve preventive action. This has been shown to be especially relevant when toxic effects damaging those defence functions of individual bodily autonomous regulation processes are becoming dysregulated by unintentional unrecognized and nevertheless irreversible neurotoxic effects. The importance of doses of variable toxicity alone of one single causal factor shrinks if cumulated or combined effects by concomitant neurotoxic damage enhance the specific morbidity outcome as such.

This applies all the more for those specific chemical structures damaging toxicologically the affected central nervous system into dysfunction, in persistingly and especially irreversibly turning an individual organism unable to enact its autonomous protective functions.

In particular the irreversible exogenic neurotoxic effects on any acquired individual susceptibility to early for age diagnosed cancer have been shown to be reflected by anteceding behavioral changes such as irritation, depressivity and suicidal ideas.

Despite various therapeutical efforts, when symptoms like the autonomous dysfunctions as part of the polyneuropathy persist after allegedly low doses of dioxins, have therefore remained uncontrolled for extended periods of time with cumulating intensity and effects.

Symptoms of exogenic depressivity are often being confused with typical endo-genic, i.e. psychiatric depression which may develop into the commitment of suicide or another sequence of events having been reportedly found in working populations exposed to dioxins. After the incident syndrome depressivity, that chronic ailment from psycho-organic origin (POS) with up to three cancer diagnoses in sequence has been found after intoxications by dioxins. These multiple clinical cancer manifestations have pointed to the observation of the stepwise and irreversibly incurring relevant dysfunctions as determining lethal outcomes.

Epidemiologic research on the mortality level as ‚diagnostic' tool counts only the final lethal tumor entity, whereas incidence studies on the level of cancer registry data including survivors reveal incurring multiple tumors being registered and reveals as additive counts in analytical studies.

Breast cancer is one tumour entity with widespread incidences with a fair likelyhood of survival, which has resulted in the underestimates of risk factors to be identified when relying on the mortality statistics as only source of evidence.

Thus, behavioral changes observed by next persons respectively bystanders may depend on attention or be weak but still reliable obvious signs, whereas prevention of the exogenic intoxication by toxic chemical risk factors, which cause irreversible neurotoxic damage - mostly involuntarily - instigate chronic deficits by external causes, which are clearly related to a cause and would eventually be preventable.

The prevention of toxic effects in working environments is thus one reasonable aim to stop earlier a threatening incriminated tendency to evolve into suicidal ideas or precocious death by early-for-age diagnosed cancer, turning out as reasonably to be one topic of ongoing research with quantitative methods.

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The role of clinical routine by neurologic screening and professional analyses as well as examinations with applied diagnostics are more and more obviously missing the relevant neuro-psychological extent of traceable specific sequelae from central nervous intoxications supposed to be preventable in the majority of cases.

When paying attention to mixtures of acute multiplying intoxications contributing to causal and irreversible effects in the long run - marked as ‚latency period' with uncertainty as to the likelihood of one causal factor in the chain of events, - the observation of a relationship as an additive sequence in occupational medicine has ben missed. Until the longterm observations from cohorts having been exposed in the chemical industry with following-up of effects contributing for more than 10 years after having been intoxicated in occupations with exogenic and highly suspicious substances, their adequate quantification associating work and disease had been missed. The neurotoxic effects of chemical intolerance on the susceptibility for chronic effects being blurred, they still are of causal relevance for both loosing not only the job and thus considered responsible for early health damage or even death, but also being omitted for long term observation by having left the job and a lack of careful medical observation by specialists for the actual late effects interrelated with death.

Those central nervous neurotoxic effects indicate irreversible behavioral changes because of an established tendency of inhaled dioxins to be stored in lipophilic structures such as the brain and nervous tissue (without liver passage) after inhalation of polluted air, which have been dismissed and/or neglected for too long.

The dioxins are known to be lipophilic and thus very unwanted by-products if showing up as unavoidable of the commercial synthesis of biocides and herbicides affecting sizeable numbers of chemical workers during their production.

An obvious example of the interaction between central nervous persistent brain damage and breast cancer has been discovered by the follow-up of young women selected for health in order to be employed in a risky production chain. These selected for health female workforces were unvoluntarily exposed in workplaces without proper exhaust and being constantly exposed for years to an environment contaminated by circulating dioxins. Biomonitoring revealed the permanent exposures.

The concomitting effects were obviously neglected since unwanted ‚byproducts' (synthetized *de novo* at 400°C) during the manufacture of herbicides such as defoliating applications and also Lindane and Hexachlorocyclohexane (HCH) during synthesis processes occurring as a syndrome. Especially the dioxins TCCD, mixed with less toxic Penta-, Hexa- up to OctaCDD, with long half-times of threatening health were neglected, i.e. no immediate and effective prevention being provided - which was the case in the years before 1980.

Ever since the Seveso-accident 1976 had shown acute and chronic irreversible effects including the increased rate of breast cancer, which apparently had been causally associated [1].

The epidemiologic approach of depicting exogenic risk factors on which preventive actions have to be focussed even requires all those methodological aspects to be applied called good epidemiologic practice.

In fact, for any successful prevention of longlasting persisting effects, the quantification of a dose-effect-relationship is a crucial must for trustworthy, mindful and helpful contributions of effective prevention. This applies especially pertinent as to so-called low dose chronic effects on the particularly vulnerable autonomous nervous system.

The dysregulation of sexual hormones as a typical as well as reliable part of that endocrine system for all involved functions, has been discovered earlier in males than among females..

The larger portion of male workers in the production enabled the research starting on mortality data by following up the workforces and collect sizeable numbers for the determination of ascertained and significant risk estimates, especialley for multiple organ locations of cancer in surviving cases.

Not at least, as soon as environmental risk factors for female breast cancer in particular within unusually early age-groups (premenopausal women) have been defined, the dimension of their specific causal contribution as carcinogenic risk factor may require actual epidemiologic results which are appearing repeatedly in several related aspects like in men.

At the beginning, the example of the discovery of risk factors for cancer in male chemical workers to this end with numerous reports of established chlorinated occupational risk factors were strengthened by the statistical analysis of those unplanned natural experiments in the human population. In those years from 1950 onwards with increasing demands for chlorinated biocides and other compounds but lack of experience on the long run, this sort of natural experiment became obligatory for progress in prevention.

The exposures occur even next to each of those living in a chemical world, but the study following the effects in the female (postmenopausal) population after the "Inferno of Calvi Risorta" near Naples, Italy, was especially interesting for the time-span until - if at all - an effective level of prevention.

To evaluate unplanned 'human experiments' has drawn attention to the ubiquitous chemical hazards during life expectancy - which also applied for women in risky jobs.

The relationship of the onset of early signs and clinical manifestation of breast cancer would have been useful for looking at the chain of events from the viewpoint of early direct environmental toxic effects on the susceptible brain. It applies all that more to the extention of insights about effects such as the toxic encephalopathy with dysfunctions of the autonomous regulation, which were barely considered at the example of missing a following-up of the 'Inferno of Calvi Risorta'. Several publications by teams starting to look within the female look at the exposed female population into an especially short latency malignant growth within the mammary gland, an organ being dysfunctionally stimulated until malignant cellular mutations -

one such cancer type affecting the mammary apocrine glandular tissue. Laboratory experiments mostly were concentrating on dermal glands of experimental animals because endocrine-stimulated glandular structures within the outer ear of rodents showed effects. The findings had rather not been up-to-date - although the opportunity was ripe. Animal experiments, which are usually well planned but followed up for short periods, although without recording the portion of developing cancers after latencies, are not comparable with the life span of human workforces with their often extreme exposures until the risk factor(s) are discovered.

The International Cohort Study in human populations at risk pointed to the significant excess mortality from neoplasms of other endocrine organs (SMR 3.60), exclusively worth those tumors of the suprarenal glands as a cause of 5 deaths to give a hint to the central nervous regulation failure as well as promoting the malignancies [2].

As the reported toxic air pollution around Naples is concerned the combustion of plastic materials as garbage in open air in the area without protective measures, which contributed to the additional risk factor. When being controlled as required by incinerators with filters, this ought to be avoided. Therefore, consequences of open air burning plastics may have been irrefutable.

Observations around the area - where the „inferno of Calvi Risorta" took place - showed an unbelievable gap of knowledge if not intentional efforts circumventing the search for evidence by obviously skipping the problem to mere theoretical considerations of cause and effect on the individual suceptibility level.

Not applied were methods to uncover possible associations between cancerogenic fumes and cancer incidences, such as shown to be effective in the successful follow-up of the Seveso population. The region where the Seveso accident had opened the eyes for the especially toxic effects of dioxins. Apparently a similar approach had not been installed respectively well enough prepared to handle any similar situation, in so far as the chemical industry was not responsible.

At the time of unrest in the Italian press it was the publication of Rosato et al. that related the metabolic syndrome (MetS) of postmenopausal women as very likely to be associated with unexpected early pre-menopausal breast cancer risk applying different index categories. However, the main question remained open: what caused the metabolic syndrome at the beginning? [3]

And why was the rise of breast cancer connected with a syndrome which was suddenly becoming of interest?

The abstract of Rosato et al. points to the sources: Studies conducted between 1983 and 2007, including 3869 postmenopausal women with incident breast cancer and 4082 postmenopausal controls admitted to the same hospitals as cases for acute conditions [3]. MetS was defined as the presence of at least three components among diabetes, drug-treated hypertension, drug-treated hyperlipidemia, and obesity.

The resulting odds ratios (ORs) of postmenopausal breast cancer were 1.33 (95% confidence interval (CI) 1.09-1.62) for diabetes, 1.19 (1.07-1.33) for hypertension, 1.08 (0.95-1.22) for hyperlipidemia, 1.26 (1.11-1.44) for body mass index ≥30 kg/m(2), and 1.22 (1.09-1.36) for waist circumference ≥88 cm. The risk of postmenopausal breast cancer was significantly increased for women with MetS (OR = 1.75, 1.37-2.22), for three or more MetS components, P for trend for increasing number of components < 0.0001) and the risk was higher at older age (OR = 3.04, 1.75-5.29, at age ≥70 years for three or more MetS components).

This study supports a direct association between MetS and postmenopausal breast cancer risk., but did not consider the origin of the 3 metabolic symptoms in the central-nervous system and thus missed to hit the chain from the typical symptomsmissed to hit the chain of events from the typical signs of a persistent syndrome due to intoxication.

This topic as part of the scientific approach which is connected to observational studies by analytical epidemiology serves pointing to a ‚public prevention problem-solving effort' and is not unimportant - especially if criminal aspects prevail, whereas the production of herbicides and biocides from chlorinated products has been promoted without control for adverse effects to workers exposed at their work-sites in an aera of discovery of very effective biocidal substances.

Mostly known in this category are the by-products of synthesis as e.g. polychlorinated carbohydrates - named dioxins as well as also some biphenylic dioxin-like PCBs- altogether proven to cause dioxin-related effects - known to be causally involved in the process of initiating or promoting cancer growth.

The dioxins are undetectable as well as unwanted by-products in any synthesis-based processes during the production of chlorinated biocides and herbicides, therefore unavoidably contaminating the process by *de novo* synthesis they are not only unpreventable - but also regularly discovered when combustion of garbage such as plastic material with temperatures around 400° C are part of the unlawful burning of disposal. As not infrequently occurring is the processing of overwhelming thrash in these days a source of chlorinated congeneres -dioxins- as long as it is not taken as a serious problem and condemned. Plastics as a source of energy is a matter of planning the future, but also for concern whether it is safe?

Concerning revelations of unplanned side effects to entire populations exposed to the fly-ashes there have to be several steps to be followed since the Love Canal experience in the USA [4].

Those polychlorinated dioxin congeners as part of the ‚dirty dozen' are hidden byproducts like ‚chlorodibenzo-congeners', such as TetraCCD and congeners Penta-, Hexa- Hepta and Octachlorodibenzodioxins known as neurotoxically persistent.

As basic material to get those effective biocides hexachlorcyclohexane (HCH, Lindane) are those of the dirty dozen products such as biphenyls meanwhile undisputed as risk factors for cancer. These have been found to be associated to increased breast cancer rates in young women, which were under risk in ages up to 50 years classified to be premenopausal.

Concluded was that Metabolic Syndrome features before clinical diagnosis indicating risk of mammary cancer. That second story of a high risk in young age-groups - an epidemiologic ongoing cohort study - shall serve as an example of quantification of a cause-effect relationship in terms of most likely risks (below).

The two related publications by Capasso et al. offered interesting findings but had different aims [5].

In 2010 the National Cancer Institute of Naples published a report by Emilia Capasso et al. "Several evidences indicate an association between *Metabolic Syndrome* and breast cancer, primarily owing to insulin resistance and low serum HDL-C" .

By altogether referring to a publication by Kabat et al. the authors drew attention to these findings on the issue of a syndrome [6]: The metabolic syndrome and breast cancer risk were already adressed but the question was left open:

Was it only the women's own decision to eat the wrong food and why and since when it started - would there be enough evidence for preventive effects?

The conclusion of Capasso et al. was [5]:
"In time-dependent covariate analyses, however, certain scenarios indicated a positive association between the metabolic syndrome and breast cancer, due primarily to positive associations with serum glucose, serum triglycerides, and diastolic blood pressure".

These were only symptoms of certified autonomous dysregulation related to a syndrome - the psycho-oganic syndrom POS, neither exciting news nor hinting to the true causes, as revealed by the WHO criteria of toxic encephalopathy.

The Italian authors suggested:
"The National Cancer Institute of Naples has pointed out the association of the metabolic syndrome and breast cancer risk in postmenopausal women.

Premenopausal women have not been included in the study group, but neither female industry workers.

Concluded was that risk Metabolic Syndrome features before clinical diagnoses present an indicator of breast cancer risk."

Any unsettlement of the hormonal arrangement - in post menopausal women - along with an increased obesity is probably favouring the hormon-dependent cell proliferation for tumorigenesis. Unsettlement of researchers has been observed since the subsequent publications made suggestive efforts?

The conclusion of the authors: Adjustment in lifestyle in postmenopause:
Whereas the food from the local sources/environment could have been affected by fly ashes, contaminated as well, this source of exposure was definitely ignored?

The urgent question was, drawing the attention to findings in Germany as results of a case-tracing survey by follow-up of a collective of women highly intoxicated by dioxins and showing extraordinary values of increased risk ratios for the specific mammary cancer related to their workplaces.

In the region of Naples with the notorious garbage combustion problems - to change only nutritional behavioural items as the only advice instead preventive action could have missed any effect, as long as the air and soil of the environment was toxically affected?

Another question to be asked has been, what reason had led to the decision, to select only postmenopausal women at all, but neither female industry workers nor control regions as particularly important sources of information for menopausal syndrome prevalences and on relevant causal factors for obesity as token.

The mention of unsettlement needs explanation insofar as: What may have been the reason of giving it a prominent position in the conclusions instead of addressing the metabolic syndrome as an indicator of urgent need for recommendations and swift action, to enhance and warning to consume toxic products from the local fields exposed to the environmental pollution.

Kabat et al. had hinted to the single clinical laboratory findings insulin resistance and low serum HDL-C by a type of 'bioavailablity stimulating the cell proliferation through specific receptors' [6].

The HDL-C was considered as an independent predictor of increased levels of several cancer-promoting hormones such as insulin, estrogens and androgens!

These observations related to another endocrine organ, the pancreas regulated by the central nervous system meant that this connection to the autonomous nervous system was to be considered as well. The association of diabetes type 2 in a young population with hexachlorocyclohexane (HCH)-uptake from imported vegetables in Saudi-Arabia has focussed new attention to the organochlorine pesticides - CNS-connection [7].

These were obvious facts meanwhile observed as a 'byproduct' in those occupationally exposed cohorts followed-up by retro- and prospective analyses of cancer incidence or at least lethal outcomes among collectives of TCDD-exposed individuals before and after the Seveso incidence.

At the Warshaw Cancer Conference on Breast Cancer and Diabetes 2013 one Ko-Author of Capasso scheduled to present the data from Naples as well as their relationship to a direct urgent environmental problem in that area around the inferno and the indication of a causal role of air pollution however, did not appear for participation. In a correspondence with the Italian Cancer Center towards that occasion to discuss with the representant the ongoing natural experiment of the likely issue of air pollution due to the "Inferno of Calvi Risorta" which had been blamed in the press, had become hence futile [8].

To relate to the garbage incineration problems around Naples, especially plastics but also other chemical but also including other chemical residues, was somehow noteworthy, because of the role the air pollution with dioxins could have played - known

as promotors and hence being especially causal occupational co-carcinogens of irreversible cancer and also associated to diabetes Type 2 (10).

TCDD as the Seveso Dioxin - but identified to be result of inferno-like burnings of plastic thrash in the Vesuvius region has been rather disturbing for the exposed population at that point in time.

The recommendation to women to "adjust their lifestyle" was out of place, since numerous press reports of dangerous environmental exposures to pyrolysis products such as the notorious garbage disposal problems - resembling somehow the ashes raining from the nearby volcano Vesuvius - had been related in the press to the "toxic waste inferno of Calvi Risorta" in the smashing touristic area of Naples.

The second publication from the same institution, however, avoided this trace by focussing on the variations of metabolic functions, i. e. the individual susceptibility of the female population: The publication „Metabolic syndrome-breastcancer link varies by intrinsic molecular subtype" by Capassso et al. in 2014, apparently hinting to individual risk factors related to Capasso's paper from 2010, did not pick up the newly suggested extreme focus to the individual men or women [9].

Instead, described were the frequencies of findings pointing to individual susceptibility of women - thus unfit to live under risk, id est - with view to the first report the message was perhaps: Unfit for the environment where they lived [5].

Contrarily, the message was changed to "New molecular biomarkers unveiling metabolic syndrome related breast carcinogenesis need to be detected to further stratify breast cancer risk by subtypes".

This approach did not consider findings in a German factory already published since 1995 with findings in a female workforce of an increased mortality from breast cancer. In contrast to the toxicokinetic approach the epidemiological follow-up referring to a scientific approach by following-up males and females in a German chemical plant manufacturing those biocides from chlorinated carbohydrate compounds containing dioxin congeners ever since the invention of the herbicide Lindan (HCH -Hexachlorcyclohehan) and others such as synthetic basis of Agent Orange'- useful for defoliating forests of Vietnam in the 70ies.

The workforce had been followed up for cancer mortality risk estimation by a cohort follow-up study since the closure of the entire production site 1984. The results were published since 1995 in several national and international reports.

Thus from the beginning of attention to the higher risk ratios for cancer and suicide as main causes of death far over expectation it was an open question, why the cancer appeared only much later than those exposures with respect to the decreasing halflife of the congeners. The number of suicides had been significantly elevated.

It was the time after the Seveso accident focussing on acute and subacute symptoms after workplace-exposures directly related to the above-mentioned psycho-organic syndrome criteria - the psycho-organic syndrome POS – meanwhile international marker for irreversible syndromatic persistent toxic encephalopathy POS-meanwhile related irreversible syndrome markers to persistent toxic encephalopathy.

The cohort approach beginning 1950 until 1984 within the production period of hexachlorocyclohexane (HCH- Lindane) provided prospectively the mortality of the workforce groups of those causes of death for males and females having been particularly specific for causal association with TCDD-exposure.

For males the overall mortality was significantly increased above expectation and especially so for malignant tumours of the airways [Table 1]. Not always, however, for those locations with low lethality, due to small observed numbers, the promotion effect on tumour progression with long latency and prognostic positive survival probability by early treatment showed effective results in that in a sizeable number of cases two organ tumours preceded the lethal third incident fatal event. In particular, suicides were significantly increased, too - possibly related to the chronic fatal diseases.

Table 1: Causes of death by standardized mortality ratios (SMR) of male workers of the chemical plant after follow-up until 2007

Causes of Death Among Men	SMR (95% CI)	Observed Cases/ Expected by Total Population
Cardiovascular Diseases	**1,16** (1,02-1,31)	**251/217,13**
Malignant Neoplasms	**1,38** (1,21-1,58)	**226/ 163,18**
Upper Respiratory Organs Cancer	**1,64** (1,32-2,03)	**88/ 53,53**
Prostate Cancer	**1,37** (0,82-2,14)	**19/ 13,90**
Total Mortality	**1,14** (1,06-1,23)	**689/ 603,42**

(bold: statistically significant)

The deaths from ‚unnatural or undefined causes' showed a significantly increased association of SMR 2.96, suspicious to contain a great part of suicides - which were not always specified enough on the death certificates because of religious constraint to certify any cause of death as selfinflicted in certain regions.

This manko, though, has to be mentioned because of the close relationship to the irreversible central nervous affections due to toxic effects accompanied by endless complaints and unbearable behavioral problems during many years. The experience of US-Army veterans having been exposed in Vietnam had developped lifelong psychotoxic effects comparable to those registered in the male cohort.

The female workforce, however, contrasted insofar as a distinctly different outcome revealed two facts [Table 2]:

The number of 390 women was selected for health to be fit for jobs in that sphere, although they were not involved in the synthetic process - and thus less likely in close contact to benzene or chlorinated carbohydrates (biphenyls) at their workplaces.

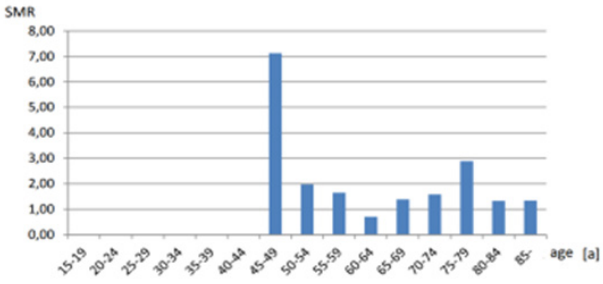
The fumes of the airborne matters, nevertheless, were present and determined environmental measurements in all supervised regions of he entire factory and nearby family living quarters.

Table 2: Causes of death by standardized mortality ratios (SMR) of 390 female workers of the chemical plant after follow up until 2007

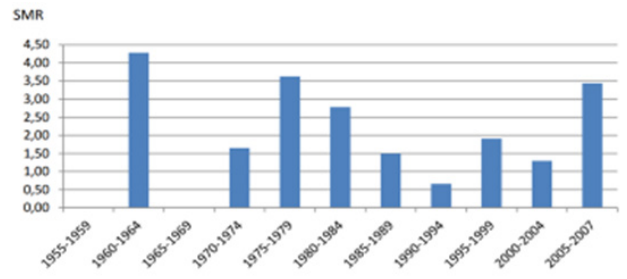
Causes of Death Among Women	SMR (95% CI)	Observed/ Expected
Cardiovascular Diseases	**0,74 (0,56-0,96)**	**58/78,33**
Malignant Neoplasms	1,17 (0,90-1,49)	65/55,70
Cancer of Upper Respiratory Organs	1,04 (0,42-2,15)	7/6,70
Breast Cancer	**1,86 (1,12-2,91)**	**19/10,20**
Total Mortality	0,90 (0,78-1,05)	180/198,90

The lower incidence of cardiovascular deaths has been an effect of the plant's own healthy worker selection by sex and was thus significantly decreased.

Women aged 15-64 had shown an increased breast cancer mortality, especially in the age-group 45-49 by a risk estimate standardized mortality ratio SMR 7 (figure 1).



Standardized Mortality Ratio (SMR) from breast cancer in 19 women (ICD-9 174)by age group (1955-2007)



Trend of Standardized Moratality Ratio (SMR) of 19 Women from 1955-2007

The one and only publication in English referring to this total sub-cohort the 180 deaths showed an overall rate of mammary tumours as cause of death SMR 1.86 (significant), whereas limited to the age group 15-64 years based significant the Standardized Mortality Rate SMR 1.21(= n.s.) was influenced by the majority of postmenopausal women among the cluster of deceased with known causes of death [10].

After age of 65 the SMR 2 indicated the increase with age, whereas for all age-groups the total SMR 1.14 (observed 41 cases, 35,83 expected) are not significant above expectation.

The splitting by age-group in the graph shows the importance of presenting those substantial differences in the younger compared to older lethal outcomes despite early detection and treatment.

In mortality studies those surviving cases because of successful treatment still being followed up are not included, contrary to incidences of all newly diagnosed cases including survivors followed-up based on cancer registries.

An additional evaluation based on an unpublished document contains the figures presented with details for breast cancer (ICD 9 174) covering the follow-up period for 1955 up to 2007.

Table 3: Mortality from breast cancer after different duration of periods with TCCD exposure risk at the workplace

Duration of Exposure	Time Period of Death	SMR (95%CI)	Observed/ Expected
≤ 1 years	1955-2007	1,84 (0,59-4,29)	5 /2,72
1-10 years	1955-2007	1,16 (0,42-2,52)	6 /5,18
≥ 10 years	1955-2007	**3,28 (1,41-6,46)**	8 /2,44 (signif.)

Increase of the risk estimate by exposure longer than 10 years during early years of production without effective prevention suggests a very strong hint and depicts the probability of a causal occupational risk due to TCCD. The prolonged follow-up still being continued until 2023 but incomplete as to this date, will show the confirmation after 16 years, apparently not influenced by survival rates from breast cancer due to medical measures [11,12].

Conclusion

The mortality of the entire cohort of 1589 German workers by evaluating the causes of death differed in that the overall main causes of death were all significantly increased for males in the production, whereas in the subcohort of 390 women, only the breast cancer risk was statistically significantly increased, by contributions from the younger premenopausal lethal cases exclusively.

This was contrasted by the decreased overall female mortality indicating a *healthy worker effect* - another strong indication of occupational risk factors being identified as most likely to be mono-causal, because the women were selected for heatlth before employment.

The plant had to be closed and dismantled in 1984, the first results were published in the time-period starting ten years later and are still followed up.

The Italian study concentrating entirely on the postmenopausal population in their sampling - because focussing on the metabolic syndrom resulted in a selection by symptoms - can therefore not be considered to be representative, let alone giving any hints as to how intense their exposure may have been.

The missing calculation of the expected numbers by a control group or regional data from a distinct area as expected control comparable to those methods used in following up the Seveso accident is reason for a lack of any evidence.

Thus, the methodological gap cannot be accepted for reasoning that the risk had been insignificant if not due to underestimation of the toxic exposures in a particular phase of representative observations which were not interpreted on the base of evidence about dioxins as main cause for central nervous handicaps with irreversible effects.

These are defined and based on criteria established by the WHO (1985) including promoting properties of dioxins as neurotoxic factor for the dysfunction of bodily repair mechanisms.

For men distinctly two malignancies of the lung and respiratory organs as well as prostate cancer were associated with significant lethality estimates substantially above high expected numbers of the control population with increasing trends.

The prostate as one of the secreting organs endocrinologically regulated by the autonomous brain centers as well as in women the glandular part of the mammary organ by promoting effect of oestrogens and stimulation by prolactin in pre-menopausal females. Loss of libido and sexual dysfunction were constant complaints of male industrial workers suffering from so-called 'psychosocial ailments' by unknow origin.

Annex

The counting unit for retrospective cohort studies of female workforce, nevertheless, is the lethal outcome for worst cases, the deceased. Two at first look unrelated observations may help to illustrate how unplanned natural experiments have to be evaluated to find the actual risk for lethal cancer if not duely prevented.

Especially the neurotoxic-exposure-effect-relationship before the precancerous carcinogenic initiating effect(s) in males after latency periods between neurotoxic symptoms such as sexual function's deficits, loss of libido in young age-groups below 35 years, is starting with vomiting, loss of consciousness at the work-place, nausea and loss of kognitive abilities as well as irreversible behavioral changes/personality changes (different from endogenic psychoses), defined by WHO as neurotoxic encephalopathy (1985). This term replaced the 'psycho-organic syndrom' as less defined entity and different from long-term persistent health outcome, such as dementia.

The examples of approaching a discovery of risky situations in Italy may be supported by an outcome in Germany according to data analysis after cause-effect associations became strong.

One approach to pinpoint a risk to a cause is related to the misinterpreted claim that allegedly low doses must be harmless as concerns the immediate damage of chemical substances. As soon as irreversible effects are observed in the long run as persistent - either as cause of suicide or cancer of the glandular organs, among other sites - the search for causal and preventable exposures is warranted.

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