Paradigm Change in the Assessment of Myeloid and Lymphoid Neoplasms Associated with Occupational Benzene Exposure (OD Number 1303)

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ABSTRACT

Benzene-caused hematologic neoplasms may be recognized as an occupational disease (OD) according to the German ordinance on ODs. At present, the OD No. 1303 covers heterogeneous diseases and various chemical agents triggering these diseases. The members of the medical advisory board specializing in ODs within the Ministry of Employment and Social Affairs recently proposed excluding "diseases of the blood, the hematopoietic and lymphatic system caused by benzene" from OD No. 1303 and classifying them as a separate OD. Benzene is generally acknowledged as a cause of acute myeloid leukemia, proven by numerous epidemiologic studies. However, there is less epidemiologic evidence of its association with other hematologic neoplasms, notably non-Hodgkin's lymphoma (NHL). To clarify this issue, the experts evaluated international literature and concluded that all kinds of myeloid and lymphoid malignancies including their prestages can be caused by occupational benzene exposure. Hence, physicians should ask patients about occupational benzene exposure and report any kind of diagnosed hematologic neoplasms, including their prestages, as suspected OD. The advisory board considered that a dose range starting from 10 ppm-years (cumulative benzene exposure) is sufficient for a > 50% probability of causing leukemias according to the WHO classification, including chronic lymphatic leukemia, and the potential preleukemias aplastic anemia and myelodysplastic syndrome, but excluding chronic myeloid leukemia (CML). For NHL and myeloproliferative diseases (including CML) the present epidemiologic evidence is considered not to be sufficient to describe a precise dose-effect relationship.

Key Words: Benzene · Occupational diseases · Hematologic neoplasms · Non-Hodgkin's lymphoma

Med Klin 2009;104:197–203.
DOI 10.1007/s00063-009-1032-8

[see source for English abstract]

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Manuscript received: July 3, 2008.
Revised manuscript accepted: January 1, 2009.

Diseases caused by occupational benzene exposure have been included in the list of occupational diseases under German law since 1925. Benzene ranks as the number one cause of malignant blood disorders recognized by industrial workers' compensation insurance carriers as occupational diseases (ODs) (432 cases from 1978 to 2003), followed by exposure to ionizing radiation (18 cases) [1]. The appendix of the current German ordinance on ODs lists benzene-caused diseases under the heading "Diseases caused by benzene, its homologs or by styrene" (OD number 1303) [2, 3]. Thus, diseases of various organ systems and noxious chemicals with different types of effects are classified under the same OD number. This fact does not do justice to the extraordinary significance of benzene-caused hematologic disorders, which make up the majority of diseases listed under this OD number. For this reason, the medical advisory board specializing in ODs within the *Bundesministerium für Arbeit und Soziales* [Ministry of Employment and Social Affairs] (BMAS) has now published the recommendation that "Diseases of the blood, the hematopoietic and lymphatic system caused by benzene" should be listed as a separate OD in the appendix of the German ordinance on ODs [4]. This overview explains the state of scientific knowledge in light of the technical discussions of the problems surrounding benzene to date and presents a summary of the medical advisory board's recommendations for attending physicians and medical experts.

Occurrence and Effect of Benzene

Before more stringent legal restrictions were put in place, benzene found widespread use as an extraction,

[see source for English abstract]

degreasing or cleaning agent and as a solvent, a component in fuels, adhesives, coating materials, surfactants, bonding agents, rubber cement, in the production of rubber and plastics, and in vulcanization. Today, benzene is still an important precursor for chemical syntheses; it is also used in chemical laboratories and found as an impurity in technical xylene and toluene [5–7]. Table 1 shows examples of relevant benzene exposures.

As early as 1971, benzene was classified by the *Deutsche Forschungsgemeinschaft* [German Research Foundation] Senate Committee for Investigating Hazardous Materials as a confirmed human carcinogen [8]. The primary target organ of benzene's carcinogenic effect is the hematopoietic system, and the majority of epidemiologic evidence that has been gathered shows that benzene causes acute myeloid leukemias (AML) [9–11]. Benzene's toxic effect usually involves damage to the hematopoietic system, although it may also affect all types of blood cells (hypo- and hyperfunctions in the erythro-, leuko- and thrombopoietic system, especially granulo-, lympho-, thrombo-, pancytopenia, aplastic anemia). The neurotoxic effect of benzene finds its way into the list of occupational diseases under number 1317 ("Poly-neuropathy or encephalopathy caused by organic solvents or their mixtures") [2, 12]. However, this overview will focus exclusively on benzene's carcinogenic effect on the human hematologic system, whose assessment involves a number of anomalies.

Legal Requirements for Assessing Causal Relationships

On October 31, 1997, the German federal government issued a new version of the ordinance on ODs based on section 9 of the *Sozialgesetzbuch* [German Social Code] (SGB) VII, last updated by the "*Verordnung zur Änderung der Berufskrankheiten-Verordnung* [Ordinance to amend the ordinance on ODs]" (BKV-ÄndV) of September 5, 2002. It specifies the diseases as ODs. Within the meaning of section 9 (1) SGB VII, ODs are "*Diseases that the federal government, through statutory ordinance, with the agreement of the Bundesrat, designates as occupational diseases, and from which the insured person suffers as a result of working in an occupation covered by insurance under section 2, 3 or 6. In the statutory ordinance, the federal government is entitled to categorize as occupational diseases those diseases that* ***according to the state of medical knowledge are caused by specific exposures to which certain groups of persons are exposed at a significantly higher level than the general population as a result of their insured occupation...***" [13]. According to Fritze et al., the requirement for recognizing a disease as an OD is that there should be double the relative risk for a disease in the exposed group in comparison to the non-exposed population [14]. This procedure is consistent with the current practice in the OD recognition process, although it is controversial [15]. Providing evidence of double the risk is difficult, especially when it involves rare diseases and exposures [4].

Accident insurance carriers conduct the investigatory procedure to determine whether an OD exists and make the decision concerning recognition. Basically, the following insurance law requirements must be satisfied for a disease to be recognized as an OD:

1. *contributing cause:* The insured occupation must legitimately be the primary reason for the damaging exposure, and
2. *proximate cause:* The damaging exposure must have caused the health damage [16].

Fact sheets for performing medical examinations of ODs are published in the German federal law gazette and serve as aids for recognizing and reporting potential ODs [3, 12]. For hematologic neoplasms, the medical assessment of causality in the OD process essentially involves determining whether benzene generally could have caused the present disease based on established scientific knowledge. It is not possible to deduce a definite threshold dose below which a carcinogenic effect can be ruled out [17]. Finding a relevant dose range that appears to be enough to cause a

hematologic neoplasm means finding a level that makes the existence of an OD sufficiently likely from an insurance law perspective.

As a general rule, competing factors that are also capable of having caused the disease must be taken into consideration when assessing casual links.

The time span between the beginning and end of exposure and the onset of the disease should also be taken into account when investigating the causal relationship [16, 18]. Benzene-caused ~~leukemias~~ hematological malignancies have a mean latency period (time span between the beginning of exposure and the time the diagnosis is made) of 32.3 years [1]. Also, the risk of developing benzene-induced acute myeloid leukemia decreases as the time since the exposure increases (so-called interim period). There is no longer any evidence of a statistically significant increased risk for AML after a period of 15 years [19].

General Capability and Biological Plausibility

The toxic and carcinogenic effect of benzene on the human hematopoietic system has been scientifically proven. The general capability of benzene to cause AML

Table 1. Examples of benzene exposure intensities (according to [4], non-exhaustive enumeration). See Table 2 for exposure times that are generally enough for sufficient evidence of causality of the OD.
OD: Occupational disease; S: shift-based exposure assessment; O: occupation-based exposure assessment – in the course of the occupational history, the technical supervisory service must be asked about the number of hours worked in that occupation (h/shift).

Extreme exposure

- Open handling of engine fuels[a] on tank ships, tanker trucks, tank cars, tank containers up to 1982 (S)
- Benzene alkylation, production of ethylbenzene in chemical plants in the GDR (in some cases up to 1990, S)
- Cleaning of objects (even washing of hands) with engine fuels[a] up to approx. 1985 (O)
- Spray application of benzene-containing coatings or surfactants before 1970 (O)
- Tar, pitch, asphalt laboratories (cold and hot extraction with benzene) up to 1980 (S)
- Cleaning of tank equipment for storing engine fuels up to 1980 (O)
- Interior cleaning of containers for storing benzene or engine fuels[a] without suitable safety measures

Moderate Exposure

- Benzene extraction, processing up to 1999 (S)
- Filling of engine fuels in tank cars and tank ships from 1990 on (S), up to 1990 (7 years, S)
- Tanker driver for engine fuels up to 1999 (S)
- Closed handling of engine fuels[a] on tank ships from 1982 (S)
- Casting and emptying of molds in a foundry (O)
- Laboratory testing of fuels (6 years, O)
- Manual application of coatings or surfactants 1970–1979 (O)

High Exposure

- By-product plant in coal chemistry (coking plant, gas plant) before 1990 (2 years, S) or before 1999 (4 years, S)
- Raw and purified benzene production before 1999 (4 years, S)
- Ethylene production up to 1990 (S)
- Operating of tanks for engine fuels by pumping, directing, mixing, opening valves, measuring fill levels, servicing and drawing laboratory samples in tanks up to 1999 (4 years, S)
- Servicing and maintaining benzene-carrying pipe parts and pumps (not automobiles) up to 1999 (4 years, S)
- Manual work on automobiles:
  - On engine fuel-carrying parts up to 1980 (2 years, O), up to 1985 (4 years, O)
  - On carburetors up to 1985 (2 years, O), up to 1990 (5 years, O)
- Cleaning of tanks for engine fuels up to 1990 (O)
- Testing function of engine fuel-carrying motor components (e.g., benzene pumps) up to 1999 (O)
- Spray application of coatings or surfactants 1970–1979 (O)

Slight Exposure

- Coking plant: working on charging cars, oven roofs, in waste gas alleys and in the die channel, petrochemistry
- Filling automobiles with benzene-containing engine fuels without a gas displacement system as filling station attendant since 1970[b]
- Cleaning of heating oil, kerosene or diesel tanks (benzene content approx. 0.004% by volume)
- Solvents from 1980 on with benzene as an impurity (maximum 0.1% by weight, typically 0.01% by weight) in all German states
- Benzene-containing solvents (> 0.5% by weight): no general information about exposure as a factor of benzene content (assess individual case)

[a] comparable hydrocarbon mixtures with regard to benzene content
[b] no measurement data are available for time periods before 1970, when some engine fuels contained significantly higher levels of benzene

is undisputed among experts and has been demonstrated in epidemiological studies [9–11]. To date it has not been clarified whether certain types of leukemia are also subject to the benzene's potential carcinogenic effect [20]. The causal relationship between occupational benzene exposure and non-Hodgkin's lymphomas (NHL), which according to the World Health Organization (WHO) classification also includes lymphoid leukemias, has long been a topic of intense scientific discussion [21]. By contrast, the general scientific consensus is that Hodgkin's lymphomas are not caused by benzene exposure. A viral genesis appears to play a key role in the causation of Hodgkin's disease [22, 23].

The current WHO classification replaced the Revised European-American Lymphoma (REAL) classification as the international standard for classifying lymphomas. Based on their cellular origin, NHL are divided into two hierarchical levels: by cell line (B- or T-cell lymphoma) and by degree of differentiation or maturity (precursor cell lymphoma or mature cell peripheral lymphoma). The WHO classification applies to all neoplasms originating from cells of the lymphatic system [24, 25].

In their benchmark review of ODs [16], Schönberger et al. list aplastic anemia, granulocytopenia to agranulocytosis, thrombocytopenia, panmyelophthisis, granulocytosis, AML, chronic myeloid leukemia (CML), myelodysplastic syndrome, osteomyelosclerosis and toxic-hemolytic anemia as potential hematologic consequences of benzene exposure. They conclude that benzene can cause any malignant hemolymphatic system disease whose cell lines develop from omnipotent stem cells. They also refer to the criterion for biological plausibility formulated by Hoffmann et al. [26, 27]. The authors argue that upon consideration of occupational medicine, toxicological and epidemiological data, and based on benzene's known mechanism of action, the development of precursor B-cell and T-cell lymphoma as a result of benzene's genetoxic effect on cells originating in the bone marrow is biologically plausible. According to the current WHO classification of NHL, these include precursor cell lymphomas (lymphoblastic lymphomas). On the other hand, the authors claim that benzene-caused "peripheral", i.e., mature cell lymphomas are not biologically plausible. "Peripheral" lymphomas include, among others, chronic lymphatic leukemias (CLL), follicular lymphoma and diffuse large cell lymphoma. Woitowitz et al. have disagreed with this hypothesis and, after a review of the scientific literature, came to the conclusion that although AML is considered the most common tumor following occupational benzene exposure based on occupational medicine-epidemiological data, lymphoid leukemias and the other subtypes of NHL are an inherent part of the spectrum of diagnoses among workers exposed to benzene. The authors argue that both animal experiment as well as non-specific and specific cytogenetic findings in humans confirm that in addition to bone marrow cell lines, those of the peripheral lymphatic system are also target and effector cells of benzene's carcinogenetic effect [17]. They argue that from this it can be concluded that peripheral NHL may also be caused by benzene. A multidisciplinary discussion of the current data on the toxic and carcinogenic properties of benzene was held at the international symposium "Recent Advances in Benzene Toxicity" in Munich in October 2004. In summarizing the outcome of the symposium, Bolt et al. conclude that more research is needed, including into the question of the manner in which tumor induction by benzene affects not only myeloid cell lines, but lymphoid cell lines as well [21]. Of the multitude of epidemiological (meta-)studies and reviews, only a few of the most significant can be summarized here:

Wong & Raabe (2000) in their meta-analysis of 26 multinational cohorts (> 308,000 mineral oil workers) found no evidence of an increased risk of dying from an NHL due to benzene exposure [28]. An analysis performed by Möhner & Heuchert (2000) including 29 cohort and 20 case studies do not support a link between benzene exposure and an increased risk of developing NHL. Based on the current data, although such a link could not be completely ruled out, it was rather unlikely from an epidemiological point of view [29]. Nold & Bochmann (2002) concluded after analyzing 35 reviews and meta-analyses, 76 cohort and 35 case studies, that no clear conclusion can be drawn about the benzene-associated risk of a certain type of leukemia [30].

Schnatter et al. (2005) concluded from their literature study (nine cohort, 13 case-control studies) that there is a highly significant risk of developing AML with a positive benzene dose-effect relationship independent of study design, especially among workers in the rubber, shoe, paint and varnish industry, who were exposed to higher levels. Although there was a trend toward an increased risk of CLL in nested case control studies, the cohort studies reviewed could not confirm this risk. The current data did not allow any conclusion to be drawn about CML and acute lymphocytic leukemias (ALL) [20]. A meta-analysis of 18 epidemiological studies by Lamm et al. (2005) yielded no indication of an increased risk of developing NHL caused by benzene [31]. In a study conducted by Glass et al. (2005) on workers in the Australian mineral oil industry, NHL and multiple myeloma (MM) were not associated with benzene exposure. In the study, though, lymphoid leukemias were categorized as leukemias and not NHL as provided for in the WHO classification. MM was also viewed separately from other NHL. The authors found an increased benzene-caused risk of leukemias (including lymphoid leukemias) with a significant dose-effect relationship [32]. Seidler et al. (2007), in their multicenter population-based case control study in Germany, were not able to demonstrate

any significant link between exposure to aromatic hydrocarbons such as benzene and developing a lymphoma [33]. Smith et al. (2007) analyzed 43 case control studies on persons with suspected benzene exposure and 26 studies with refinery workers. The authors concluded that on the whole the studies supported a link between occupational benzene exposure and NHL, although a large portion of the study results were not statistically significant [34]. Steinmaus et al. (2008) in their meta-analysis of studies of both benzene exposure and refinery workers found, based on the higher relative risks, evidence that benzene causes NHL [35].

Limited Significance of Epidemiological Studies

With potentially long latency periods between the beginning of exposure and the time of diagnosis, by the time the investigations are conducted there is rarely any reliable exposure data on conditions at workplaces that often date back several decades. The extremely small number of epidemiological studies is therefore subject to serious uncertainties about exposure estimates, and disease risks are over- or underestimated. That workers are often exposed to multiple chemicals also makes it more difficult to single out purely benzene-related effects.

Over the years, the nomenclature of myeloid and lymphoid malignant diseases has undergone constant change. The current international standard is the method recommended by WHO for classifying tumors of the hematopoietic and lymphatic system [25]. The ICD-GM coding [36] preferred by epidemiologists up to now does not properly correspond to the WHO classification. The cytogenetic, immune phenotyping and molecular biological diagnostic methods available today allow much more precise subtyping of hematological neoplasms than was the case in previous years. Some of the cases from earlier studies would have led to different diagnoses from today's perspective. Comparing studies that use different classifications is difficult, if even possible at all. For instance, lymphoid leukemias that are categorized as NHL according to the WHO classification were usually included in a group with myeloid leukemias in past studies. For rare diseases, as most NHL subtypes are, one would expect to see very small numbers of cases in cohort studies. This therefore significantly limits the possibilities of epidemiological studies: It is so unlikely for a disease to occur, that it is impossible to get a sufficiently large random sampling of workers exposed to benzene on the job to prove a double risk. The medical advisory board specializing in occupational diseases within the BMAS concluded that studies that already did not show any increased risk for AML or acute non-lymphoid leukemias (ANLL) would certainly not be suitable for providing evidence of rarer, malignant neoplasms of the hematopoietic system, especially NHL. In such cases, it is likely that the subjects groups were not exposed to sufficient levels of benzene. A meta-analysis by the medical advisory board therefore only included epidemiological studies that, as an expression of relevant benzene exposure, showed an increase of the relative risk for AML or ANLL of ≥ 2.0 (double the standardized mortality rate, the standardized incidence rate or the relative risk). The relative risks of these studies yielded weighted estimators for the meta-relative risk (mRR): For lymphomas as a whole (not including Hodgkin's disease) and for MM there was statistically

Table 2. Examples of sufficient benzene exposures for Group 1 and Group 2 occupational diseases (according to [4]). CLL: chronic lymphoid leukemia; CML: chronic myeloid leukemia; NHL: non-Hodgkin's lymphoma; WHO: World Health Organization.

Group 1		Group 2	
Probability of causation > 50% in the range of approx. 10 ppm years epidemiologically confirmed or plausibly inferable: • Leukemias according to WHO (not including CML) and CLL • Aplastic anemia • Myelodysplastic syndrome[a] • Precursor cell lymphoma		As a general rule, individual assessment of exposure (no epidemiology-based quantification): • NHL (except CLL, precursor cell lymphoma) • Myeloproliferative diseases[a] (including CML)	
Exposure Intensity (see Table 1)	**Duration (Years)**	**Exposure Intensity (see Table 1)**	**Duration (Years)**
Extreme	1	Extreme	2–5
High	2–5	High	≥ 6
Moderate	6–10		
Slight	Assessment of individual case		

[a] The medical advisory board did not explicitly classify all cases of CMML (chronic myelomonocytic leukemia) under one group. According to the WHO classification, CMML is a borderline case because, depending on the individual manifestation, it represents a spectrum of disorders with predominantly myelodysplastic to predominantly myeloproliferative characteristics [d. V.]

significant (5% confidence level) evidence of an increased risk (lymphoma: mRR = 1.55; 95% confidence interval [CI]: 1.08–2.23 and MM: mRR = 2.29; 95% CI: 1.21–4.34). For NHL narrowed to several main groups (ICD-9 200 [lymphosarcoma and reticulum cell sarcoma] and 202 ["other neoplasms of lymphoid tissues"]) the calculated risk estimator mRR = 1.63 (95% CI: 0.98–2.71) was not statistically significant. From an analysis of the epidemiological study results, the authors concluded that occupational benzene exposure from an occupational medicine-toxicologically significant level (dose) can not only cause AML, but NHL and MM as well [4].

Discussion of the Dose-Effect Relationship of Benzene

Hoffmann et al. (2001) derived a risk estimate for the development of benzene-caused leukemias from the results of the "Pliofilm cohort" study. This well-studied cohort was made up of 1,165 employees of a rubber manufacturer in the USA who were exposed to high levels of benzene during the production of rubber hydrochloride (so-called Pliofilm) between 1936 and 1975 [26, 37–45]. To quantify the cumulative benzene exposure, the exposure is expressed in ppm years. 1 ppm year is equivalent to the amount to which a worker is exposed at a workplace with 1 part benzene per million parts air over 1 year. The authors found a statistically significantly increased risk of developing acute leukemia from a benzene dose of 200 ppm years and up. For > 40 to < 200 ppm years, they found that it was reasonable to make an individual assessment, taking into consideration expected values for latency period, duration of exposure and individual exposure conditions based on occupational medicine experience. For ≤ 40 ppm years, they concluded there was no evidence of an increased probability of developing a disease [26].

Woitowitz et al. (2003) critically disagreed with the risk ranges selected by Hoffmann et al. and claimed that even cases with cumulative exposures of significantly < 40 ppm benzene years require a qualified assessment to determine whether there is sufficient evidence of causality, taking into account any relevant peculiarities in the individual case [17]. Glass et al. (2005) in their study of employees from the Australian mineral oil industry found a strong link between leukemias and moderate benzene exposure > 16 ppm years (cumulative exposure) or at dose levels of > 0.8 ppm for the occupation with the highest exposure level [32]. The medical advisory board within the BMAS, after an in-depth analysis of international studies, concluded that according to the current state of scientific knowledge, a range of 10 ppm benzene years and up has been shown to have a causation probability > 50% for certain diseases (see Table 2, Group 1). The first it includes among these, based on epidemiological results, are the leukemias according to the WHO definition (exclusive of CML) and CLL. It claims the risk is also plausible for the early and pre-stages of AML and ANLL, since these diseases were usually classified under one group in these studies, i.e., for myelodysplastic syndrome and aplastic anemia. Due to the vulnerability and proliferation of hematopoetic stem cells, the authors conclude that stem cell-related NHL (precursor cell lymphoma) demonstrates the same risk as the diseases mentioned above. For the remaining hematological neoplasms, i.e., peripheral NHL (except CLL) and myeloproliferative diseases within the meaning of the WHO (see Table 2, Group 2) the authors state that the following applies: As a general rule, an individual assessment must be made since in these cases the epidemiological evidence regarding the risk increase is not sufficiently reliable. Factors that should be taken into consideration in these cases are, among other things, poor work hygiene conditions and particularly intensive skin contact (cleaning of skin with benzene, occlusive conditions), heavy physical labor with increased inhalation, exposure peaks, an extraordinarily long duration of exposure and a juvenile exposure age. The technical supervisory service of the relevant accident insurance carrier is responsible for the detailed investigation of the exposure. Table 1 shows examples of occupations with extreme, high, moderate or slight exposure intensities. Table 2 gives examples of benzene exposures that, depending on the intensity and duration of exposure, are generally enough to satisfy the requirement of sufficient evidence of causation for the diseases listed under Group 1 or 2, and thus for recognition as an OD (causation probability > 50%) [4].

CONCLUSION

In a bulletin dated September 1, 2007 [4], the medical advisory board specializing in occupational diseases within the BMAS recommended that "diseases of the blood, the hematopoietic and the lymphatic system caused by benzene" be classified under a separate number in the appendix to the German ordinance on occupational diseases. The significance of epidemiological studies of benzene's causation of certain hematologic neoplasms is limited, especially due to low incidence rates and uncertain exposure estimates. Nevertheless, after reviewing the international literature, the medical advisory board came to the consensus that all malignant tumors of the myeloid and lymphatic system and their pre-stages can be recognized as ODs. In light of the scientific discussion and the previous practice of recognition, this well thought-out conclusion—although it cannot be verified in a strictly statistical sense from an epidemiological standpoint—confirms a paradigm shift in social medicine for the assessment of relationships in myeloid and lymphoid benzene-caused diseases. For this reason, if a patient has a history of occupational benzene exposure, physicians should report any kind of hematologic cancers, including their pre-stages, as suspected OD. Starting from a range of 10 ppm benzene years, a > 50% probability of causing leukemias according to the WHO classification (excluding CML), CLL, aplastic anemia, myelodysplastic syndrome and precursor cell NHL is to be expected. Due to the lack of

should generally perform an individual assessment of cases of other types of NHL and myeloproliferative diseases.

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