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Benzene-induced Cancers: Abridged History and Occupational Health Impact

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Abstract

Benzene-induced cancer in humans was first reported in the late 1920s. Carcinogenesis findings in animals were not reported conclusively until 1979. Industry exploited this “discrepancy” to discredit the use of animal bioassays as surrogates for human exposure experience. The cardinal reason for the delay between first recognizing leukemia in humans and sought-after neoplasia in animals centers on poor design and conduct of experimental studies. The first evidence of carcinogenicity in animals manifested as malignant tumors of the zymbal glands (sebaceous glands in the ear canal) of rats, and industry attempted to discount this as being irrelevant to humans, as this organ is vestigial and not present per se in humans. Nonetheless, shortly thereafter benzene was shown to be carcinogenic to multiple organ sites in both sexes of multiple strains and multiple species of laboratory animals exposed via various routes. This paper presents a condensed history of the benzene bioassay story with mention of benzene-associated human cancers.

Keywords

benzene; carcinogenicity; industry influence; history; bioassay; public health; occupational safety; primary prevention

Further to Peter Infante’s excellent investigative exposé of the truth behind some of the benzene industry’s malpractices and abuses (e.g., withholding incriminating data) and resultant OSHA standard-setting issues,[1] there were similar shenanigans surrounding the experimental findings from benzene-exposed animals. Following a series of early, albeit patently inadequate, bioassay experiments on benzene—too few animals, lack of control animals, low and short-term exposures, incomplete pathology often looking only for leukemias[2]—the more modern animal bioassay data clearly confirm and extend the possible cancer hazards of worker and consumer exposures to benzene. To complement the feature by Infante,[1] a brief history of benzene bioassays is given, accompanied by mention of human cancer findings.

CARCINOGENESIS BIOASSAYS

Experimental chemical carcinogenesis bioassays are designed and carried out to identify potential carcinogenic hazards and likely effects for humans.[3] Carcinogenesis results in rodents—mainly rats and mice—have been shown to be consistent and reliable indicators of human cancer risks. All known human carcinogens that have been evaluated in animal bioassays are also correlatively carcinogenic. Further, of the nearly 100 recognized human carcinogens, about one third were shown first to be carcinogenic in experimental animals and subsequently in humans.[4] Hence, for chemicals discovered to be carcinogenic to

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laboratory animals, prudent public health policy suggests strongly that eliminating or minimizing exposures to these carcinogens would reduce environmentally and in particular occupationally associated cancers. Today, this primary prevention strategy serves unfortunately only as a dim beacon of better times when the health of workers was more prominent than profit. This has evolved into what is now referred to as the precautionary principle,[7–9] which poses to act earlier in the available albeit scanty data stream to initiate health safety strategies and proactive occupational and public health measures, despite possible scientific uncertainties.[10]

IARC BENZENE EVALUATIONS

Over the years, the International Agency for Research on Cancer (IARC) has evaluated benzene on three occasions: 1974,[11] 1982,[12] and 1987.[13] In 1974,[11] the IARC decided "The data reported do not permit the conclusion that carcinogenic activity has been demonstrated" based on "Benzene has been tested only in mice by subcutaneous injection and skin application." Regarding human carcinogenicity data, IARC noted "It is established that exposure to commercial benzene or benzene-containing mixtures may result in damage to the haematopoietic system. A relationship between such exposure and the development of leukaemia is suggested by many case reports, and this suggestion is strengthened by a case–control study from Japan."

In 1982[12] IARC evaluated benzene as having "sufficient evidence that benzene is carcinogenic to man," but the available animal data on benzene as only "limited evidence of carcinogenicity in experimental animals." This animal-data conclusion was based on:

> Benzene has been tested in rats by intragastric administration and inhalation exposure, and in mice by skin application, inhalation exposure and subcutaneous injection. Oral administration to rats resulted in an increase in the incidence of Zymbal-gland carcinomas. Anaemia, lymphocytopenia and bone-marrow hyperplasia and an increased incidence of lymphoid tumours occurred in male mice exposed by inhalation to benzene; in similar inhalation studies with another strain of mice and with rats there was no evidence of a leukaemic response. Experiments involving skin application or subcutaneous injection of benzene did not produce evidence of carcinogenicity, but most of these experiments were inadequate.

The last time IARC evaluated benzene was in 1987,[13] with evidence of carcinogenicity considered sufficient both for humans and for animals. In humans the evidence was based on increases in leukemia in benzene workers.[14,15] In animals, according to IARC

> Benzene was tested for carcinogenicity in mice and rats by several routes of administration. Following its oral administration at several dose levels, it induced neoplasms at multiple sites in males and females of both species. After mice were exposed to benzene by inhalation, a tendency towards induction of lymphoid neoplasms was observed. Exposure of rats by inhalation increased the incidence of neoplasms, mainly carcinomas, at various sites. Skin application or subcutaneous injection of benzene to mice did not produce evidence of carcinogenicity, but most of the experiments were inadequate for evaluation. In a mouse-lung tumour bioassay by intraperitoneal injection, an increase in the incidence of lung adenomas was observed in males.

Since the 1987 IARC evaluation, more confirmatory epidemiologic information has become available,[16,17] with multiple myeloma,[18] lung cancer, and non-Hodgkin's lymphoma[19–23] now clearly attributable to benzene exposures. Risks of acute myeloid leukemia and other malignant and nonmalignant hematopoietic disorders associated with benzene exposure in China are consistent with known benzene exposures, hematotoxicity, and cancer risks,

extending evidence for hematopoietic cancer risks to levels substantially lower than previously established.[24] From global public health and occupational perspectives, perhaps IARC should consider updating its 20-year-old benzene and cancer evaluation. Granted the human and animal data are considered already to be at the highest level of concern, new cancer sites have been discovered and the carcinogenesis correlations between animals and humans are mechanistically worth re-examining.

MALTONI AND CHEMICAL BIOASSAYS

From his early cocarcinogenicity studies of croton oil on rabbit skin[25] and DMBA on hamster skin,[26] through seminal bioassays of vinyl chloride,[27–29] gasoline products,[30,31] including benzene and MTBE,[32,33] and formaldehyde,[34] up to consumer chemicals such as ethyl alcohol,[35] one can justifiably track the early history of chemical carcinogenesis by following Cesare Maltoni and his colleagues' dedicated work on identifying occupational carcinogens[36–38] for developing public health and occupational standards and polices of primary prevention of human cancers.[39]

BENZENE BIOASSAYS

Following Maltoni and his colleagues' seminal finding of the carcinogenicity of benzene to laboratory animals in 1979,[40] they and others more definitively elucidated the carcinogenesis of benzene in a series of papers[41–47] using their unique bioassay exposure design with various experimental protocols.[36–38]

Near the beginning of Maltoni's efforts evaluating benzene for carcinogenesis in animals the National Toxicology Program,[3,48–55] created by David Rall,[56,57] also embarked on unraveling the enigma of why benzene appeared to be an exception (along with arsenic[58–64]) to the mammalian carcinogen paradigm[2,65–67]; that is, a chemical known to cause cancer in humans had not been found to do so similarly in animals.* In this vein, I remember being contacted persistently by industry to learn of early results of our bioassays on benzene. This was a bit amusing, because we already knew that benzene caused cancers (leukemias) in humans, and I wondered why the concentrated interest of industry in our animal findings. Calls came at least weekly from the chemical and petroleum industries. Finally one frequent caller told me that if the bioassays were negative then the industry would have some mammalian biologic means to better challenge the human epidemiologic findings, which industry was already confronting. If our bioassay were clearly negative this would help bolster their argument that other chemical exposures and workplace circumstances (confounders) would lend credence to their benzene-is-not-the-culprit rationale. In keeping with the NTP's open policy I responded with new pathology information as it came available, reminding the inquisitors that until the data were peer-reviewed in public session, our findings could only be considered preliminary. When our pancarcinogenesis findings confirmed and complemented Maltoni's, industry was seemingly taken aback, and momentarily puzzled regarding their next strategy.[68–70]

Carcinogenesis results of 21 mutually tested chemicals including benzene were compared between the Ramazzini Foundation and the NTP, finding remarkable concordance of overall results, and identifying a combined total of 13 target sites of benzene-induced carcinogenesis in animals[67] (Table 1).

*Both of these "exceptions" have been appropriately debunked, solidifying the inexorable correlation that all known human carcinogens that have been tested in laboratory animals are likewise carcinogenic.[3,71–77]

In 1928, Delore and Borgomano[78] reported the first human case of leukemia associated with benzene exposure.[2,65,78] Prior to 1928, of course, benzene was known to cause "benzene poisoning," a sequela typically involving bone marrow damage. Chronic benzene poisoning among workers leads to various blood disorders such as leukopenia, agranulocytosis, anemia, pancytopenia, aplastic anemia, myelodysplastic syndrome (MDS; preleukemia), and leukemias.[24,79–81] More recently, occupational exposures to benzene have been causatively linked with multiple myeloma,[18] non-Hodgkin's lymphoma,[23] acute[82,83] and chronic[84–87] lymphocytic leukemia, chronic myelogenous leukemia,[82,83] and at lower exposures,[24,84,87] with some indications for lung cancer.[19–21] All of these and additional target sites have been identified in animals as well.[2,47,65,67] Another prime use of chemical carcinogenesis results allows the identification of other potential presumptive target sites that may be added to or looked for distinctly in epidemiologic investigations.

Speculatively, perhaps other sites of human carcinogenicity have not been either looked for or seen in benzene-exposed workers because death from leukemia is relatively rapid after onset and diagnosis. This could also be because available benzene cohorts individually have been small, except for the one in China. Humans showing the later-aged or latency-occurring lung cancers likely escaped developing leukemias.[13,16,19–21] This concept of competing risks of cancer is shown experimentally quite nicely with the potent carcinogen 1,3-butadiene: as exposure concentrations are lowered different tumor patterns become manifest.[88,89] As with benzene or other chemicals, early lethal tumors such as lymphocytic lymphomas or leukemias often reduce the number of animals at risk for expressing later-developing and -occurring neoplasms at other sites. The same, of course, pertains to humans exposed to different exposure levels, patterns, and durations.

Before, at, and subsequent to Maltoni's first reports of clear evidence of benzene carcinogenicity in laboratory animals (and arsenic as mentioned above), intense industry propaganda and pressure attempted to discount long-term animal bioassays as being irrelevant to human risk identification; this strategy certainly had much to do with stifling evidence of benzene carcinogenicity, and extended to many other economically important chemicals showing positive cancer findings in animals as well.[3,69] For some years before the benzene issue, industry and others had mounted a strenuous effort to dismiss the value of bioassays in a concerted global attempt to continue unabated marketing and use of chemicals shown to cause cancers in laboratory animals, and not yet examined epidemiologically.[90]

To justify its basic premise, industry seized and campaigned on the then-notion that arsenic and benzene were both considered to be carcinogenic to humans and yet had not been shown to cause cancer in laboratory animals. Now that these two temporarily, albeit historically non-concordant chemicals have been tested adequately in animals and shown to be classic and multifarious carcinogens (benzene[2,47,65,67]; arsenic[57–64]), this once-dynamic duo touted by industry for vested purposes no longer serves its needs (see footnote on page 214). Now industry uses other arguments such as those based on threshold differences,[91] "non-genotoxic" carcinogens,[92,93] mechanisms or "modes-of-action" being unique to animals and not relevant to humans,[91–100] even hormesis,[101,102] cell proliferation,[92,192–109] inflammation and general toxicity,[110–112] hormonal mediation,[113–115] mouse liver tumors,[116] and benign tumors,[117] to name a few obfuscatory issues industry has latched onto to cloud bioassay results and impede or derail regulatory actions.

Additionally, Maltoni's first findings of benzene cancer induction in animals[40,41] were heavily disputed by industry because the organ affected by cancer was the zymbal gland (located in the inner ear canal), which humans have as a vestige. This issue of zymbal glands has been addressed and debunked, along with other so-called "rodent-unique" organs susceptible to benzene-induced carcinogenesis.[118] Fortunately, this issue became moot

given the plethora of tumors and tumor types and organ sites seen in the benzene studies. The other issue making the benzene-is-safe argument less tenable, as with arsenic, was that benzene was already long known to be carcinogenic to humans. If this had not been the case, the battle for more stringent and better worker protection and reduction of occupational standards for acceptable exposure levels would have been even more difficult. As it was, lowering of the occupation exposure standard took ten years longer than anticipated because of adverse decisions issued by the U.S. Supreme Court.[119]

We witness this animal-only argument every single time a chemical of some economic importance is found to cause cancer in laboratory animals in the absence of epidemiologic data. What we never encounter is industry's questioning or disputing the many "negative" bioassay results on big-volume chemicals.

BENZENE METABOLITES

Mammalian metabolism of benzene is complex, with multiple pathways and diverse metabolites. Despite abundant research, neither the most active carcinogenic metabolite(s) nor a detailed well-accepted mechanism(s) of carcinogenicity of benzene is known with even a modicum of certainty.[2,120,121] Tsutsui et al.,[120] for example, studied benzene- and key metabolite-induced cell transformation, gene mutations, chromosome aberrations, aneuploidy, sister chromatid exchanges, and unscheduled DNA synthesis in Syrian hamster embryo cells. They found an array of effects for these endpoints but no one metabolite of benzene consistently drove the results. Another way to shed light on those is to investigate carcinogenicity of individual metabolites. Fortunately, several of the most abundant or long-lasting metabolites (or those that could be gotten in sufficient quantity) have been tested for carcinogenic activity: catechol, hydroquinone, and phenol. The designs and findings for these carcinogenicity studies are summarized.

Catechol

Naturally occurring in fruits and vegetables, present in cigarette smoke, and an industrial chemical, catechol is used to make insecticides, perfumes, drugs, and polymerization inhibitors. Catechol has been used as an antiseptic, in photography, and in dyestuffs.

Catechol has been shown to have strong promoting activity in mice, and alone induces forestomach hyperplasia, generally a few papillomas of the forestomach (non-glandular), and adenomatous hyperplasia and adenocarcinomas of the glandular stomach in near all rats.[122–126] Administered with known carcinogens, catechol typically increased the occurrence of initiator-targeted tumors of the forestomach and stomach, tongue, and esophagus, but did not enhance their occurrence in liver, urinary bladder, or thyroid.[122–126] Thus, catechol exhibited strong cancer-promotion activity.

Hydroquinone

Used an antioxidant in the rubber industry, as a developing agent in photography, and as an intermediate in the manufacture of rubber and food antioxidants and monomer inhibitors, hydro-quinone products are also used as depigmenting agents to lighten skin. Hydroquinone in deionized water was given by gavage for two years to groups of rats and mice of each sex, five days per week at 0, 25 (rats), 50, or 100 (mice) mg/kg.[127,128] Nephropathy was common among the rats, with hyperplasia of the renal pelvic transitional epithelium and renal cortical cysts increased in male rats. In mice, thyroid follicular cell hyperplasia was increased (males: 9% vs 28% and 35%; females: 24% vs 85% and 82%). Increases of anisokaryosis, multinucleated hepatocytes, and basophilic foci occurred in the livers of male mice.[127,128]

Regarding carcinogenic responses, renal tubular cell hyperplasia was seen in two top-dose male rats, with dose-related increases in renal tubular cell adenomas in 0% vs 7% and 15%. Mononuclear cell leukemia in female rats was increased: 16% vs 27% and 40%. In low-dose male mice liver tumors were marginally elevated: 36% vs 54% & 45%, whereas in female mice liver tumors were intensified in both hydroquinone groups: 5% vs 29% and 24%.[127,128]

Hydroquinone made available to rats and mice of both sexes at 0.8% in the diet for two years induced renal tubular cell hyperplasia as well as adenomas, mainly in males of both species, and was associated with chronic nephropathy in rats.[129] Also, epithelial hyperplasia of renal papilla was increased in male rats. Hepatocellular adenoma was enhanced in male mice. Squamous-cell hyperplasia of the forestomach epithelium was higher in mice of both sexes given hydroquinone, but no increase in tumor development was observed.[129]

Thus, hydroquinone caused kidney tumors in male (and possibly in female) rats and mice, leukemia in female rats, thyroid follicular cell hyperplasia in mice, and liver tumors in male and female mice.[127–130] Overall, there is clear evidence that hydroquinone causes cancer in laboratory animals.

Phenol

Approximately 90% of phenol is used in the manufacture of phenolic (phenol formaldehyde) resins, caprolactam, bisphenol A, alkyl phenol, and adipic acid. The remainder is used to produce an assortment of products: salicylic acid, phenacetin, dyes, metal cleaners, disinfectants, antiseptics, photographic chemicals, wood preservatives (pentachlorophenol), paints, paint and varnish removers, and agricultural chemicals (2,4-D and parathion).[131]

For two years rats and mice of each sex were given drinking water containing 0, 2,500, or 5,000 ppm phenol. The only carcinogenic response was increases in leukemia, 36% vs 62% and 50%, that may have been associated with the phenol administration.[131,132] Even though the NTP considered an association with administration of phenol was not established, the incidences in both exposure groups were greater than in controls and the low dose showed a statistically significant effect. No other carcinogenic response was observed in rats or mice. Other low dose increases in male rats included C-cell tumors of the thyroid (8% vs 14% and 2%), adrenal gland pheochromocytomas (26% vs 44% and 18%), and interstitial-cell tumors of the testes (88% vs 98% and 94%).[131,132]

In other studies, phenol given orally with benzo(a)-pyrene produced sixfold increases in malignant tumors of the forestomach over BaP given alone.[112] Phenol also promoted mouse skin carcinogenesis in two-stage protocols.[133]

Scientific evidence indicates that multiple mechanisms are likely to contribute to benzene-induced leukemias and cancers in other target organs; whether these include individual or co-mechanisms for the individual metabolites remains to be ascertained. (Reasonably straightforwardly, this of course tends to represent universal thinking in chemical carcinogenesis, and leads to the notion that unique chemicals or classes of chemicals induce cancers by “different” mechanisms.) Increasing information lends further credence that metabolites of benzene are primarily responsible for its carcinogenic activity.[2,120,121,134–137] Phenol, hydroquinone, and catechol are the major metabolites of benzene in mammals, established in analyses of human urine,[135] and have been tested for long-term carcinogenicity. Phenol, to a lesser extent, and hydroquinone are associated individually with inducing leukemia in animals, and we might opine in humans as well. One wonders what would be the result(s) if the two chemicals were tested together; that is, whether these findings would be more or less potent than those for benzene or either of these metabolites

alone. Catechol causes forestomach and stomach tumors in animals, whereas benzene causes forestomach tumors but does not cause stomach tumors. Some of the other carcinogenic effects of benzene may be due to combinations of the metabolites or to others not yet evaluated for carcinogenic activity.

At the same time, carcinogenic concordance in target sites between animals and humans need not be sacrosanct. Typically in animals there are more tumor sites identified simply because more pathology is done on animals than on humans. One suspects that if all organs were evaluated in humans when people died of “old age” or with cancers other organs would be found to be neoplastic as well. Meanwhile, epidemiology might best broaden the organ scope for future studies.

CONCLUSIONS

The clear findings of cancers in animals resulting from exposures to benzene (and to arsenic), and to all other known human carcinogens that have been tested in animals, confirm and validate once again the value of long-term animal bioassays for identifying potential cancer risks to humans.[3,5,67–77,138–173] Virtual acknowledgement of this led industry to new strategies to deny bioassay results: posing that mechanisms (or “modes of action”) of carcinogenesis in animals are unique and hence not relevant to humans. Interestingly most of these claims are based on supposition and not data regarding either the exact mechanism in animals or the lack thereof in humans. A key to reducing damage from all carcinogens, whether identified in animals or in humans or in both mammalian species, centers on reducing exposures.

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TABLE 1

Benzene: Organ/Tissue site Tumors Identified in Studies from the Ramazzini Foundation and the National Toxicology Program* in Seven Experiments Using Three Strains of Rats and Three Strains of Mice

	Sprague-Dawley Rats (Gavage)	Sprague-Dawley Rats (Inhalation)	Wistar Rats (Gavage)	Fisher* Rats (Gavage)	Swiss Mice (Gavage)	RF/J Mice (Gavage)	B6C3F1* Mice (Gavage)	
Zymbal gland	+	+	+	+	+	−	+	6
Mammary gland	[+]	[+]	−	−	+	+	+	5
Oral	+	+	+	+	−	−	−	4
Lung	−	−	−	−	+	+	+	3
Nasal cavities	+	[+]	+	−	−	−	−	3
Lymphoma	[+]	−	−	−	−	+	+	3
Liver	+	[+]	−	−	−	−	+	3
Forestomach	+	−	−	−	−	−	[+]	2
Skin	+	−	−	+	−	−	−	2
Uterus	−	−	−	−	−	−	+	1
Ovary	−	−	−	−	−	−	+	1
Harderian	−	−	−	−	−	−	+	1
Preputial gland	−	−	−	−	−	−	+	1
All malignant	+	+	+	+	+	+	+	7
Total SITES	9	6	4	4	4	4	11	

+ = positive carcinogenic response; [+] = marginally increased carcinogenic response; − = no significant carcinogenic activity; sites listed in order of prevalence of responses per organ/tissue.

*The two strains utilized in the NTP studies.

Source: Huff.[56]