BENZENE AND NON-HODGKIN'S LYMPHOMA – AN ANALYSIS OF THE LITERATURE

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Summary: **A** review of the epidemiological case-control and cohort literature has been conducted for evidence of an association between benzene exposure and non-Hodgkins' lymphoma (NHL). Fifty-nine NHL case-control studies were located, eight of which reported on benzene exposure. Five were population-based studies, and three were occupational cohort-based studies. Seven of the eight case-control studies reported odds ratios that hover near 1.0 (range 0.5-1.2). The eighth study (nine cases of lymphosarcoma among male rubber workers) showed statistically significant associations between NHL and each of four non-benzene solvents (carbon disulfide, carbon tetrachloride, hexane, and xylenes) but not with benzene. Five benzene cohort studies reported risk estimates that included lymphomas, four cohorts in **US** industries and one in China. None of the cohorts had a significant excess of NHL mortality. The four **US** cohorts together had 12 cases where **9.9** were expected. The Chinese study, with a statistically non-significant excess NHL mortality, showed no dose-response relationship to benzene exposure (range: < 10 to > 400 ppm-yrs). Thus, neither the case-control literature nor the cohort literature demonstrates an association between benzene and non-Hodgkins' lymphoma.

Keywords: Benzene, Non-Hodgkin's Lymphoma, Epidemiology,

Introduction:

Benzene is well-known both as an industrial chemical and as a toxic agent to the hematopoietic system. It is classified as a human carcinogen by professional and governmental agencies, primarily based on the evidence associating occupational exposures to benzene with acute myelogenous leukemia and its variants (AML). We have conducted a systematic review and analysis of the epidemiological literature to assess the specificity of the association between occupational exposure to benzene and the various neoplasms of the hematopoietic and lymphopoietic tissues (NHLT) (9^{th} International Classification of Diseases codes **200-208).** Careful analysis of the epidemiological literature on benzene and the leukemias demonstrated that AML was the only leukemia found consistently to be in excess with significant **benzene exposure** (Lamm et **al.,** 1989). The dose-response relationship was shown to be strongly non-linear. The evidence did not demonstrate an association between benzene exposure and either acute lymphocytic leukemia, chronic lymphocytic leukemia, or chronic myelogenous leukemia. Two case series, (Torres et al., 1970; Aksoy et al., 1984) and two epidemiological studies, (Decouffle et al., 1983; Rinsky et al.,

1985) in the 1970s and the 1980s had suggested that benzene exposure might be a risk factor for multiple myeloma. An analysis of the population-based and hospital-based case-control literature was conducted that indicated that benzene exposure was not a likely causal factor for multiple myeloma (Bezabeh et al., 1996). Similarly, a meta-analysis of benzene exposed petroleum worker cohorts, (Wong and Raabe, 1997) found no increased risk of multiple myeloma in a combined cohort **of** more than *250,000* workers. Three studies reported data on various lymphomas and on mixed exposures that include benzene. (Girard and Revol, 1970) found no association for either **NHL** or HD and benzene and/or toluene exposure. (Vianna and Polan, 1979) reported that New York State males 45 and over who died either from lymphosarcoma, reticular cell sarcoma, or Hodgkins's Disease (HD) were more likely to have had a job with presumed exposure to benzene and/or coal tar; however (Smith and Norelle-Lickiss, 1980) found no such association between NHL and HD and similar benzene-related occupations for men of any age in Tasmania, Australia. We have conducted an extensive review **of** the case-control literature on non-Hodgkin's lymphomas (NHL) to determine what chemical exposures appear to be related to **NHL** and have then focused on those studies that reported on the association between

benzene and **NHL.** We have then examined the literature and data from cohort studies of benzene-exposed workers to assess for consistency in the benzene/NHL association between the case-control and the cohort literature.

Materials and Methods:

A bibliographic search was conducted to identify case-control studies on NHL. The National Library of Medicine MEDLINE database was searched from **1966** through **1998** to identify NHL case-control studies. These articles were obtained, and their references were searched to identify additional studies. Published reviews on NHL were also examined to seek among their references studies not previously identified. In total, **59** case-control studies on NHL were identified, obtained, and analyzed.

Each study was examined to determine the reported exogenous exposures considered potentially as risk factors for NHL. Much of the literature focused on risks to cosmetologists or risks associated with the use of hair dyes. Additional literature attempted to identify significantly associated factors for NHL among agricultural populations. The third body

of literature reported on associations with industrial chemicals and industrial processes. From this body of literature, we identified eight NHL case control studies that reported on exposure to benzene among the study subjects.

The number of cases and the number of controls were identified for each study, and the reports of exposure were abstracted. Where the data existed, each case and each control was classified as either exposed or unexposed for each **of** the exposure variables. Odds ratios with 95% confidence limits (adjusted or unadjusted) were abstracted from the reports where they existed or were calculated from the data where they did not. The odds ratio, the odds of a case having been exposed compared to the odds of a control having been exposed, was used as the measure of association. 95% confidence limits that excluded the value 1.0 (using a two-tailed Poison distribution) were used as the definition of statistical significance.

Neoplasms of the hematopoietic and lymphopoietic tissues (NHLT) are comprised of the leukemias [ICD code 204-2081, multiple myeloma (MM) [ICD code 203], and the lymphomas [ICD codes 200-2021. The

lymphomas include both Hodgkins' disease (HD) [ICD code 201] and **NHL** [ICD code 200 and 202]. NHL includes lymphosarcomas, reticulosarcomas, and other lymphomas. Where the number of observed cases and expected cases were not reported for a particular diagnostic category, they were obtained or estimated from the available data.

Results:

Case-Control studies

Eight **NHL** case-control studies reported benzene exposure among their study subjects. None of these studies were primarily directed to seeking an estimate **of** the association between NHL and benzene exposure, but all eight provided information from which that association could be assessed. The specifics of these studies follow.

1. (Bernard et al., 1984) reported a case-control study of etiological factors in lymphoid malignancies based on 285 newly diagnosed lymphoma or lymphatic leukemia cases and their controls from six health districts in the

Yorkshire (UK) health region from October **1979** through December **1981**. Expert review of pathological diagnoses and validation of interview information by cross-checking with hospital records contributed to the quality assurance of this study. The control group was selected from hospitalized patients without malignancy, while cases were ascertained from registry records and active surveillance of clinicians and laboratories involved in managing lymphatic malignancies. Controls were chosen as 1:1 matches for age, sex, and geographic area and were interviewed. Investigated factors included past medical events, occupations, and certain social factors. The odds ratios for benzene use among **81** male NHL cases and their controls and among **29** male Hodgkins' Disease (HD) cases and their controls were reported The odds ratio and **95%** confidence limits.for benzene exposure and NHL was **0.49 (95%** CI - **0.21-2.00)** and for benzene exposure and HD was **1.00 (95%** CI - **0.50-1.50).**

2. (Blair et al., **1993)** reported an evaluation of occupational and industrial exposures from a case-control study based on **622** NHL cases in white males in the agricultural areas of Iowa and Minnesota. Interviews of subjects were conducted in **1980-83.** Statistically significant adjusted odds

ratios were reported for workers from industries characterized as special industrial machinery **(SEC** code 355), real estate (651), and personal services (72). Thirty-two different industrial codes and thirty different occupational codes showed non-significant associations with OR> 1.5 based on two or more cases. No significant associations were observed for specific occupations. Metals was the only one of twenty-one selected potential exposures that showed a statistically significant adjusted odds ratio for NHL (OR = 1.13; 95% CI - 1.01-1.6). The odds ratio for benzene exposure was 1.1 (0.9-1.4). These odds ratios had been adjusted for age, state, smoking, family history of malignant lymphoproliferative diseases, agricultural exposure to pesticides, use of hair dyes, and direct or surrogate respondent. The adjusted odds ratio for higher intensity benzene exposure [1.5 (95% CI - 0.7-3.1)] was somewhat great than for lower intensity benzene exposure **[**1.1 ***(95%*** CI - 0.8-1.4)**]**

3. (Fritschi and Siemiatycki, 1996) reported on occupational factors in **a** case-control study based on 23 multiple myeloma cases, 54 Hodgkin's Disease cases, and 215 NHL cases newly diagnosed in Montreal males in 1979-85. They reported statistically significant associations for multiple

myeloma and more than ten years employment as sheet metal workers, for Hodgkin's Disease and more than ten years employment as a performing or graphic artist or with substantial exposure to fabric dust, or waxes or polishes, and for NHL and more than ten years in the textile industry or with substantial exposure to copper dust, ammonia, plastic pyrolysis products, fur dust, or cotton dust. The adjusted odds ratio for NHL and substantial exposure to benzene was 0.8 (95% CI - 0.3-2.1) and for NHL and non-substantial exposure to benzene was 0.7 (95% CI - 0.4-1.1). Thus, no association was found between NHL and benzene exposure. Similarly, no association was found between NHL and solvent exposure.

4. (Scherr et al., 1992) reported on occupational exposures identified in an NHL case-control study conducted in the metropolitan Boston area from January 1980 through May 1982 and based on 303 cases and their age and gender matched controls. Measures of association were examined for ten different specific exposure agents, including benzene. The relative risks ranged between 0.8 and 1.8, and none of them was statistically significant. The relative risk for benzene exposure was 1.2 (95% CI - 0.5-2.6).

5. (Schumacher and Delzell, 1988) conducted a case-control study based on 501 death certificates for males in North Carolina certified as dying from NHL in the years 1968-70, 1975-77, and 1980-82 and matched non-cancer deaths. Exposure assessments were based on industry and occupation information from the death certificates. Increased risks were observed for white males in professional, technical, and managerial occupational groups and in black males in machine trade occupational groups. NHL risk was significantly associated with social class for white males, with risk increasing from lower social class to upper social class. No association was found between NHL and employment in the textile industry or as farmers or as laborers. No association was found between NHL and occupations with exposure to asbestos or to benzene based on an occupational-exposure linkage system developed at Harvard University with the National Cancer Institute. Fifty-six cases and 67 controls were coded as benzene-exposed among the white males and 10 cases and 21 controls among the black males. Adjusted for age and year of death, the benzene exposure odds ratio for NHL was 0.77 (95% CI - 0.56-1.07) in white males and 0.94 (95% CI - 0.47-1.87) in black males.

6. (Greenland et al., 1994) conducted site-specific case-control analyses for cancer deaths among active and retired white male employees of a large transformer-assembly facility in Massachusetts. All cohort members were employed during 1946-84 and died during 1969-84. A significant and robust association was found for lung cancer and resin system exposure. There were 15 lymphoma deaths (including lymphomas, lymphosarcomas, and reticulosarcomas) among the 512 cancer deaths with job histories. There were 1202 control (non-cancer) deaths with job histories. The benzene exposure odds ratio for the lymphoma deaths and their controls was 1.00 (95% CI - 0.22 to 4.53).

7. (Ott et al., 1989) reported the results of a case-control analysis of lymphatic and hematopoietic tissue (NHLT) cancer in a USA chemical manufacturing environment which included 52 **NHL** cases. Controls were randomly selected on 5:1 ratio to cases. Exposure odds ratios were examined for 111 work areas, 52 chemical activity groups, and 21 specific chemicals. Significant associations were observed for **NHL** cases among men who worked in the ethanol unit and among instrument men and foremen in the maintenance and construction work areas. Significant

associations were also observed for **NHL** cases among men who worked in the alkyl sulfates or high toxicity metal salts chemical groups. The benzene-exposure odds ratio for NHL cases and their controls was **1.00 (95%** CI - **0.3-2.3).**

8. (Wilcosky et al., **1984)** examined solvent exposure relationships in a case-control analysis of specific cancer deaths occurring in **1964-73** within a **6678** member cohort in a rubber and tire-manufacturing plant. Solvent-specific exposure odds ratios were calculated for each of 20 solvents and for each of four cancer groups among white males, including stomach, respiratory, prostate, lymphosarcoma and reticulum cell sarcoma (n=9), and lymphatic leukemia. For lymphosarcoma and reticulum cell sarcoma, the age-adjusted exposure odds ratios were statistically significant for exposure to carbon disulfide, carbon tetrachloride, hexane, and xylenes with odds ratios of **3.7-5.6.** The odds ratio for benzene of **3.0** was not statistically significant. No confidence limits were calculated. Benzene was not significantly associated with any of the cancers.

Table 1 presents the epidemiological characteristics of the eight NHL case-control studies which report benzene exposure. It gives the study design characteristics and the exposure/outcome ascertainment methods for each. Five of the eight studies were population-based, representing a mixture of urban and rural areas. Four of the population-based studies used interviews to assess exposures, while the remaining study relied on occupation and industry information from the death certificates. NHL cases were identified through a combination of mechanisms, including reports from registries, hospital surveillance, medical records, and death certificates.

The three additional industry-specific studies represented nested case-control evaluations of NHL within cohorts of workers from transformer assembly, chemical, and rubber manufacturing plants, respectively. These studies primarily relied upon death certificate reports for case ascertainment and on industry work history records for individual exposure estimates.

Table **2** presents the study subject counts, the data on benzene exposure, and their analyses for each of the eight NHL case-control studies that reported benzene exposure. The eight case-control studies presented

twelve benzene exposure odds ratios. The odds ratios and their 95% confidence intervals are presented as the measure of association. These analytic results are also demonstrated in Figure 1.

Table **2** and Figure 1 demonstrate that the odds ratios from the various studies cluster about the value of 1.0, revealing no evidence of an association between NHL and benzene exposure in the case-control studies. Both Table **2** and Figure 1 also demonstrate the 95% confidence intervals for the studies. Three studies show odds ratios less than one, two show odds ratios of one, and three show odds ratios greater than one. None of the studies showed a statistically significant association between NHL and benzene exposure. The case-control literature provide no evidence of an association between NHL and benzene exposure.

Cohort studies

Many of the benzene-exposure cohort studies report the leukemia mortality but do not report having examined the lymphoma mortality of that

cohort. Five benzene-exposure cohorts (four from the **US** and one from China) have been identified that do report on their lymphoma mortality.

1. (Decoufle et al., 1983) reported the mortality experience through 1977 of 259 males ever employed in white- or blue-collar jobs at a petroleum refinery/chemical manufacturing plant during 1947 through 1960. Subjects included all males identified from the employment rosters of the central office. The three females on the rosters were not included in the analysis. The 259 males contributed 5,942.5 person-years of observation to the analysis. Sixty-three deaths were observed, ten **of** which were from cancer. Four deaths from NHLT were observed where 1.06 were expected ($p < 0.05$). Three deaths were from leukemia where 0.44 were expected ($p < 0.01$). The fourth NHLT death was from MM where 0.17 would have been expected. The expected death count from MM was calculated by noting that the residual expected mortality from non-leukemia NHLT was 0.62 [1.06 minus 0.44 = 0.621 and that 27% of non-leukemia NHLT mortality among white males in the **SEER** 1973-1977 mortality tables is due to MM [0.62 x 0.27 = 0.171. Thus, the expected mortality count for lymphomas was 0.45 [0.62 minus 0.17 = 0.45, although none were observed. **As** 79% of the

lymphoma mortality among white males in the SEER 1973-77 mortality tables is due to NHL, the expected mortality count for NHL was 0.36 [0.45 x 0.79 = 0.361. This benzene-exposure cohort showed no NHL mortality where 0.36 cases were expected (SMR = 0.00; 95% CI - 0.00-10.25).

2. (Bond et al., 1986) reported the mortality experience through 1982 of 956 white males identified on plant census lists as having worked for at least one month in any of three production areas between 1938 and 1978 with 98.4% follow-up and 24,571 person-years of observation. These workers were employed in either the chlorobenzyl, alkyl benzene, or ethyl cellulose operations. Four leukemia deaths were found where 2.1 were expected (SMR = 1.94; 95% CI - 52-488). All four were myelogenous. Two lymphoma deaths were observed where 1.8 were expected (SMR = 1.11; 95% CI - 0.13-4.01). Both lymphoma deaths were from lymphosarcoma or reticulosarcoma (ICD 200) where 1.1 were expected (SMR = 1.80; 95% CI - 0.22-6.57). Adjustment of the expected NHL cases to include ICD 202 using the US male mortality rates for 1969 yields an NHL expected of 1.55 (SMR = 1.29; 95% CI - 0.16-4.66).

3. (Wong, 1987) reported the mortality experience between 1946 and 1977 of 4,602 male chemical workers from seven plants with at least six months exposure to benzene with 98% follow-up and 133,968 person-years

of observation. Twenty-two (22) NHLT deaths were observed where 24.36 were expected **(SMR** = 0.90; 95% CI - 0.57-1.37). Four (4) lymphosarcoma and reticulosarcoma deaths were observed where 3.55 were expected **(SMR** = 1.12; 95% CI - 0.31-2,89). Seven NHL deaths were observed where 5.12 were expected **(SMR** = 1.37; 95% CI - 0.55-2.82) Wong, (1998).

4. (Infante et al., 1977) reported the initial findings of the National Institute for Occupational Safety and Health (NIOSH) study of benzene-exposed workers at two "Pliofilm" industrial sites in Ohio. The study **of** these plants has provided the major base (and the major controversy) for the assessment of health risk from benzene exposure. NIOSH reported a significant excess leukemia mortality among the approximately 748 white males defined as having had at these plants at least one day of exposure to benzene during 1940-1949. (Infante et al., 1977) reported the results of mortality experience through June 1975 when the mortality follow-up was 75% complete, and (Rinsky et al., 1981) reported it when mortality follow-up was 98% complete. Seven leukemia cases were observed where 1.25 were expected ($p < 0.001$). All seven leukemias were myelo- or monocytic.

(Rinsky et al., 1987) expanded the cohort to the 1165 white men with at least 1 ppm-day of cumulative exposure to benzene through 1965 and extended the follow-up through 1981. They reported a significant excess risk of leukemia mortality (Observed = **9,** Expected = 2.7, and Ratio = 3.37, **p** < 0.01) and of MM mortality (Observed = 4, Expected = 1.0, and Ratio = 4.09, p < 0.05).

Rinsky and his colleagues further expanded the cohort to 1212 white males and extended the follow-up through 1987 for a total of 40,345 person-years of observation. These data were published by (Paxton et al., 1994) who demonstrated a significant excess risk of **NHLT** mortality (Observed = 21, Expected = 9.51, Ratio = 2.21, p < 0.05) and of leukemia mortality (Observed = 14, Expected = 3.89, Ratio = 3.60, p < 0.01). (Wong, 1995) demonstrated from the same data set a non-significant excess risk of MM (Observed = 4, Expected = 1.37, Ratio = 2.91, p > 0.05) that was not dose-related to benzene exposure. The expected death count from lymphomas was calculated to be 4.25 [9.51 minus 3.89 minus 1.37 = 4.251, of which 3.37 would have been due to NHL [4.25 x 0.79 = 3.371 and 0.88 due to HD [4.25 x 0.21 = 0.881. Three cases of **NHL** were observed where 3.37 cases

were expected *[SMR* = **0.89; 95%** CI - **0.18-2.60].** Wong **(1998)** made a similar calculation using the ***OCMAP*** statistical program and reported for this study population three cases of NHL with an expected **of 3.28** (SMR= **0.91; 95%** CI – **0,19-2.67).**

Table **3** examines the NHL risk in the **US** benzene cohorts. (Decouffle et al., **1983)** found no NHL case where **0.36** were expected. (Bond et al., **1986)** found two lymphoma deaths where **1.55** were expected. (Wong, **1987)** found seven NHL cases where **5.12** were expected. The NIOSH study with follow-up through **1987,** (Paxton et al., **1994;** Wong, **1995, 1998)** found three NHL cases where **3.28** were expected. Two of the **US** benzene cohort studies had odds ratios < **1.0;** two had odds ratios > **1.0.** Among the four **US** studies, **10.3** NHL deaths were expected, and **12** were observed **(Ratio** = **1.16; 95% CI, 0.60-1.91).** Thus, the **US** benzene-exposed cohorts show no significant association between NHL and benzene exposure.

The analysis of the Chinese benzene cohort is presented separately since the data systems differ. The methodologies for collecting data and comparing to **US** mortality rates is similar across the **US** benzene cohort

studies. The methodologies for the Chinese study have been more recently developed by the study participants.

5. The Chinese Academy of Preventive Medicine (CAPM) and the National Cancer Institute (NCI) have been conducting an epidemiological mortality study of 74,848 industrial workers ever exposed to benzene during 1972-1987 and 35,805 industrial workers not exposed to benzene during 1972-87 in 12 cities in China. Eligible workers were identified from monthly salary records of 672 factories using benzene and 40 factories not using benzene. Unexposed workers came either from the 40 factories not using benzene or from non-benzene exposure areas of 69 of the benzene-using factories. The benzene-exposed workers came from a number of industries, including printing, painting, shoe manufacturing, pesticide, and chemical manufacturing. Few uniquely had benzene exposure; the largest group of workers came from the paint industry – either paint manufacturers or paint applicators.

(Yin et al., 1996a, 1996b) reported significant or borderline significant relative risks for AML (3.1), leukemia (2.3), lymphoma and related disorders (4.5), non-neoplastic diseases of the blood (infinite), lung cancer

(1.4), all cancers (1.2), and all causes (1.1). (Hayes et al., 1996) examined the dose-response relationship of cancer mortality by benzene exposure and reported a significant positive trend for all cancers, lung cancers and hematopoietic malignancies. Those analyses used the unexposed cohort as the referent category. (Hayes et al., 1997) provided revised case counts and demonstrated a non-statistically significant increased relative risk for NHL of 3.0 (95% confidence limits, 0.9-10.5) in comparison to the non-benzene cohort (Table 4). The exposures in the Chinese benzene cohort had been grouped into five strata (<10, 10-39, 40-99, 100-399, and 400 + ppm-yrs), each of which had about the same expected NHL mortality. The data in Table 4 show the relative NHL mortality in each benzene exposure strata in the benzene-exposed cohort (< 10 ppm-yrs through > 400 ppm-yrs), using the lowest exposure group (< 10 ppm-yrs) as the referent category. These are presented graphically in Figure 2.

Discussion:

The epidemiological literature for assessing an association between Non-Hodgkin's Lymphoma and benzene exposure have been reviewed. The case-control studies and their characteristics have been identified (Table 1).

Their data and results have been shown (Table 2), and their odds ratios are seen to cluster about 1.0 (Figure 1). The **US** cohort studies have been identified and their risk estimates demonstrated (Table **3).** Their pooled risk estimate is 1.16 (95% CI, 0.60-1.91).

Figure 2 demonstrates the absence of a dose-response curve within the benzene-exposed cohort with the NHL mortality distributed among the exposure strata rather independent of the magnitude of exposure with the possible exception of those categorized as having exposures of 400 ppm-yrs or greater. Such exposures would exceed the current **US** occupational exposure limit by a factor of ten.

Table 4 indicates both that the NHL risk in the benzene-exposed cohort appears to be greater than that in the non-benzene exposed cohort and that the NHL risk in the benzene-exposed cohort is not dose-related to the cumulative benzene exposure. These findings are open to a number of interpretations. (Hayes et al., 1997) presented analyses indicating that the association is limited to benzene exposure occurring at least ten years prior to diagnosis. This analysis, however, was based on data from the external

non-benzene exposed Chinese cohort as the referent group rather than on the low exposure group within the Chinese benzene-exposed group. Interpretation of this hypothesis will have to await within cohort trend analysis and then case-control analysis examining both the full range of exposures experienced in the workplaces and the non-occupational risk factors.

Our counter hypothesis is that future analysis may demonstrate that some exposure other than benzene is a more likely causal association with NHL in the cohort defined **or** labeled as a benzene cohort. Such a finding would be similar to the findings of the University of North Carolina (UNC) rubber worker studies with respect to lymphocytic leukemia (as opposed to lymphoma). The UNC studies originally published that there was a significant association between chronic lymphocytic leukemia (CLL) and benzene exposure (Arp, et al., 1983). However, in subsequent study after specific exposures to all solvents were determined, they found that five non-benzene solvents were significantly associated with CLL cases but that benzene was not, (Wilcosky, et al., 1984; Checkoway H, et al., 1984). Interpretation of the **NHL** findings in the Chinese benzene cohort will have

to await their completion of the full exposure analysis of workers. As in the UNC study, some non-benzene solvents may well explain the NHL risk in the benzene cohort.

Review of the five cohort studies, this include one with no NHL death, three with non-significant risk ratios of about one, and one with a non-significant risk ratio of about three and no dose-response relationship between NHL and cumulative benzene exposure. In total, these three cohort studies do not show an association between NHL and benzene exposure.

Conclusion:

Review of the case-control literature on benzene and NHL fails to find evidence of an association between benzene and NHL. Similarly, the epidemiological cohort literature does not demonstrate an association between the two. Thus, the epidemiological literature does not support an association between NHL and benzene exposure.

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