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# ORIGINAL ARTICLES

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## Risk of Laryngeal Cancer by Occupational Chemical Exposure in Turkey

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Laryngeal cancer is the second most common cancer among men in Turkey. In this hospital based case-control study, we evaluated laryngeal cancer risks from occupational chemical exposures. We analyzed 940 laryngeal cancer cases and 1519 controls. Occupational history, tobacco, and alcohol use and demographic information were obtained by a questionnaire. The job and industries were classified by special seven-digit codes. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) based on a developed exposure matrix for chemicals, including diesel exhaust, gasoline exhaust, polycyclic aromatic hydrocarbons (PAHs), formaldehyde, and solvents. An excess of laryngeal cancer occurred with diesel exhaust (OR = 1.5, 95% CI = 1.3–1.9), gasoline exhaust (OR = 1.6, 95% CI = 1.3–2.0), and PAHs (OR = 1.3, 95% CI = 1.1–1.6). There was a dose-response relationship for these substances with supraglottic cancers ( $P < 0.000$ ). The PAH association only occurred among those who also had exposure to diesel exhaust.

### Introduction

Laryngeal cancer is the second leading cancer among men in Turkey <sup>[1]</sup> and is responsible for about 7% of all deaths among men in the country. <sup>[2]</sup> Age-standardized incidence rate of laryngeal cancer in men is 11.52 per 100,000, which is about double of the world rate (5.69 per 100,000). <sup>[3]</sup> Although alcohol and tobacco consumption are the most important factors in the etiology of laryngeal cancer, occupational and environmental factors also play a role. <sup>[4][5][6]</sup> Previous studies showed that exposure to various dusts and chemicals have been associated with an increased risk of laryngeal cancer, <sup>[7][8][9][10]</sup> but few have been conducted in developing countries. <sup>[11][12][13]</sup> In our previous reports on the occupational risk factors of laryngeal cancer, we founded excess risks among several occupations, particularly for supraglottic laryngeal cancer among those potentially exposed to silica and cotton dust. <sup>[14][15]</sup> We observed an increased risk of laryngeal cancer among drivers, textile workers, and production workers, <sup>[14]</sup> jobs that might have a variety of exposures. To further evaluate these findings, we developed a job exposure matrix (JEM) for several chemical exposures in Turkey: diesel exhaust, gasoline exhaust, polycyclic aromatic hydrocarbons (PAHs), formaldehyde, and solvents. These chemicals were selected because of a high probability of exposure in Turkey and previous associations with laryngeal and oropharyngeal cancers in the literature. <sup>[7][8][10][16][17]</sup>

## Methods

We selected the study population from the Oncology Treatment Center of the Social Security Agency Okmeydani Hospital, Istanbul, Turkey, between 1979 and 1984. The center provides cancer treatment to workers in the Marmara region, which is the northwest part of Turkey, and also to some workers in other regions. Upon admission to the hospital, all patients responded to a standardized questionnaire, administered by trained interviewers, seeking information on occupational history, tobacco, and alcohol use. Details of the data collection method have been explained elsewhere. <sup>[12][18]</sup> An oncologist from the hospital reviewed the records of patients for diagnostic verification and coded them according to the International Classification of Diseases for Oncology (ICD-O) classification system. <sup>[19]</sup> We used four-digit ICD-O codes of laryngeal cancers to classify tumors by location: glottic (161.0,  $n = 227$ , 24.1%), and supraglottic tumors (161.1,  $n = 438$ , 46.6%) were analyzed separately, but subglottic (161.2) and non-classified (161.9) cancers were combined ( $n = 275$ , 29.3%).

Among the 7631 cancer cases admitted to this hospital between 1979 and 1984, there were 958 diagnosed with laryngeal cancer. After excluding subjects with incomplete information on age, smoking, alcohol, job titles, industry titles and tumor site, as well as women ( $n_{\text{cases}} = 7$ ), there were 940 male laryngeal cancer cases available for analysis. As controls, we selected all male patients with Hodgkin's disease ( $n = 202$ ), soft tissue sarcoma ( $n = 130$ ), and cancers of nonmelanoma skin ( $n = 657$ ), testis ( $n = 219$ ), bone ( $n = 66$ ), male breast ( $n = 34$ ), and series of noncancer subjects (benign pathologies,  $n = 211$ ) for a total of 1519 controls. These patients were included in the control group because they are thought not to share similar etiologic factors with laryngeal cancer. Two hundred eleven noncancer control patients were initially diagnosed with cancer and admitted to the Okmeydani Hospital for treatment, where they were re-evaluated and diagnosed with benign pathologies.

We coded occupations and industries according to a modification of the Standard Occupational Classification (SOC) and Standard Industrial Classification (SIC) system. <sup>[20]</sup> An industrial hygienist (Dr Dosemeci) who had an extensive experience in occupational settings in Turkey, completed JEM exposure assignments for the seven-digit SOC and SIC codes to provide a more detailed classification of jobs and industries. <sup>[14][21]</sup> For each occupation and industry, we assigned exposure intensity and probability levels for diesel exhaust, gasoline exhaust, PAHs, formaldehyde, and solvents, according to a scale of 0 to 3 (0 = none, 1 = low, 2 = medium, and 3 = high exposure). For intensity assignments,

exposure intensity of the substance of interest was 1 = lower than threshold limit value (TLV), 2 = between the TLV and two times of the TLV, 3 = greater than two times of the TLV. For probability, we assigned exposure probability of the workers for a substance of interest as 1 = lower than 25%, 2 = between 25 and 75%, and 3 = greater than 75% in a given occupational and industrial categories. We then combined occupational and industrial exposure scores using the following algorithms: If the exposure was dependent on occupation only, we calculated the final score by algorithm based on SOC (intensity = intensity<sup>2</sup><sub>soc</sub>; and probability = probability<sup>2</sup><sub>soc</sub>). If the exposure depended on occupation and industry, the exposure score was assigned by multiplying the SOC- and SIC-based assignments (intensity = intensity<sub>soc</sub> × intensity<sub>sic</sub>; and probability = probability<sub>soc</sub> × probability<sub>sic</sub>). We classified final scores as: no exposure (score 0), low (score 1–2), medium (score 3–4), and high (score 6–9) exposures. During the exposure assignment process, case or control status of individuals was masked. Details of the exposure assessment procedures have been reported elsewhere. [21] [22]

We used unconditional logistic regression analysis in SPSS 10.1 to calculate odds ratios (ORs) and 95% confidence intervals (CIs) adjusted for age, smoking, and alcohol. We used likelihood ratio analysis to test model fit. We tested model fit for each model for “exposure–cancer location” pairs based on the probability level of 0.05. Because of limited available quantitative smoking and alcohol data for cases (46.6% and 13.6%, respectively) and controls (32.0% and 7.3%, respectively), we controlled our analysis by “ever use” of tobacco and alcohol. We also evaluated the effect of quantitative smoking (pack·years) data on our results. We also used Mantel-Haenszel test to analyze relationship between laryngeal cancer and occupational exposures. Because we have observed similar results, in this article we presented logistic regression analysis.

## Results

The mean age was 52.9 ± 10.3 for laryngeal cancer cases and 47.1 ± 15.4 for controls. Among cases 73.9% were smokers and 24.5% regularly consumed alcohol. Smoking and alcohol consumption were less common among controls (58.6 and 13.4%, respectively). Age-adjusted laryngeal cancer ORs for, ever smokers and ever alcohol consumers were 1.7 (95% CI = 1.4–2.1) and 2.0 (95% CI = 1.6–2.6), respectively.

The most prevalent exposure among laryngeal cancer cases was PAH (40%), followed by diesel exhaust exposure (32%). Workers with potential exposure to diesel exhaust, gasoline exhaust, and PAHs had excess risk of laryngeal cancer (Table 1). We also evaluated the relationship between exposures to diesel exhaust and PAHs. All people exposed to diesel exhaust also were classified as exposed to PAHs, and after excluding diesel exhaust-exposed individuals, the age, smoking, and alcohol-adjusted OR for laryngeal cancer among PAHs exposed workers was 0.8 (95% CI = 0.6–1.1).

**Table 1. Risk of Laryngeal Cancer by Exposure and Anatomic Location of Tumor\***

<b>Exposure (Ever/Never)</b>	<b>All Cases</b> OR (95% CI) <i>n</i> <sub>cases</sub> / <i>n</i> <sub>controls</sub>	<b>Supraglottic</b> OR (95% CI) <i>n</i> <sub>cases</sub> / <i>n</i> <sub>controls</sub>	<b>Glottic</b> OR (95% CI) <i>n</i> <sub>cases</sub> / <i>n</i> <sub>controls</sub>	<b>Others</b> OR (95% CI) <i>n</i> <sub>cases</sub> / <i>n</i> <sub>controls</sub>
Diesel exhaust	1.5 (1.3–1.9) 297/339	1.5 (1.2–1.9) 137/339	1.7 (1.2–2.3) 76/339	1.5 (1.1–2.0) 84/339

Gasoline exhaust	1.6 (1.3–2.0) 220/235	1.5 (1.1–2.0) 95/235	1.8 (1.3–2.5) 57/235	1.8 (1.3–2.4) 68/235
Polycyclic aromatic hydrocarbons	1.3 (1.1–1.6) 376/486	1.3 (1.1–1.7) 174/486	1.4 (1.0–1.9) 94/486	1.3 (0.9–1.7) 108/486
Formaldehyde	1.0 (0.8–1.3) 89/146	1.0 (0.7–1.5) 42/146	1.2 (0.8–2.0) 25/146	0.9 (0.5–1.4) 22/146
Solvent	0.8 (0.7–1.0) 271/531	0.9 (0.7–1.1) 136/531	0.7 (0.5–1.0) 58/531	0.8 (0.6–1.1) 77/531

\* Age, smoking, and alcohol adjusted.

ORs by exposure intensity levels and anatomic localization of laryngeal tumors are presented in [Table 2](#). A dose-response relationship occurred between supraglottic cancers and exposure to diesel exhaust ( $\chi^2_{\text{trend}} = 17.6, P < 0.001$ ) and PAHs ( $\chi^2_{\text{trend}} = 10.1, P = 0.001$ ). Although there were no high-level gasoline exhaust exposed cases, we observed a dose-response relationship between low- and medium-level gasoline exhaust exposed groups for all laryngeal cancers ( $\chi^2_{\text{trend}} = 22.1, P < 0.001$ ) and for supraglottic cancers ( $\chi^2_{\text{trend}} = 10.4, P = 0.001$ ). No exposure-response pattern was evident for other anatomic locations, except a slight negative trend in glottic cancers with diesel exhaust exposure intensity ( $\chi^2_{\text{trend}} = 4.77, P = 0.029$ ). Supraglottic tumor also showed a significant dose-response relationship with probability of exposure to diesel exhaust ( $\chi^2_{\text{trend}} = 14.1, P < 0.001$ ; [Table 3](#)).

**Table 2. Risk of Laryngeal Cancer by Exposure Intensity Levels and Anatomic Location of Tumor**

Exposure Intensity	All Cases	Supraglottic	Glottic	Others
	OR (95% CI) <i>n</i> <sub>cases</sub> / <i>n</i> <sub>controls</sub>			
Diesel exhaust				
Low	1.5 (1.1–1.8) 161/185	1.2 (0.9–1.7) 64/185	2.0 (1.4–2.9) 52/185	1.4 (1.0–2.0) 45/185
Medium	1.7 (1.2–2.3) 91/101	1.8 (1.2–2.7) 46/101	1.3 (0.8–2.4) 17/101	1.8 (1.1–2.8) 28/101
High	1.6 (1.0–2.4) 45/53	2.0 (1.2–3.2) 27/53	1.0 (0.4–2.3) 7/53	1.3 (0.7–2.6) 11/53
Gasoline exhaust				
Low	1.5 (1.2–2.0) 141/154	1.3 (0.9–1.8) 57/154	2.0 (1.3–2.9) 43/154	1.6 (1.1–2.3) 41/154
Medium	1.8 (1.3–2.5)	1.8 (1.2–2.8)	1.4 (0.7–2.5)	2.2 (1.4–3.5)

	78/81	38/81	14/81	27/81
High	–	–	–	–
Polycyclic aromatic hydrocarbons				
Low	1.4 (1.1–1.7) 189/234	1.2 (0.9–1.6) 78/234	1.8 (1.3–2.5) 59/234	1.3 (0.8–1.8) 52/234
Medium	1.3 (1.0–1.6) 138–189	1.4 (1.0–1.9) 68/189	1.0 (0.6–1.6) 26/189	1.4 (1.0–2.0) 44/189
High	1.5 (1.0–2.2) 49/63	1.7 (1.1–2.8) 28/63	1.1 (0.5–2.3) 9/63	1.2 (0.6–2.3) 12/63
Formaldehyde				
Low	1.1 (0.8–1.5) 82/124	1.2 (0.8–1.7) 40/124	1.3 (0.8–2.1) 21/124	1.0 (0.6–1.6) 21/124
Medium	0.5 (0.2–1.3) 6/19	0.3 (0.1–1.5) 2/19	0.9 (0.3–3.3) 3/19	0.3 (0.0–1.9) 1/19
High	0.7 (0.1–7.1) 1/3	–	3.2 (0.3–32.2) 1/3	–
Solvent				
Low	0.7 (0.5–0.9) 97/202	0.8 (0.6–1.1) 50/202	0.6 (0.3–1.0) 19/202	0.7 (0.5–1.1) 28/202
Medium	0.9 (0.7–1.2) 124/228	0.9 (0.7–1.3) 56/228	1.0 (0.7–1.5) 30/228	1.0 (0.7–1.5) 38/228
High	0.8 (0.5–1.1) 50/101	1.0 (0.7–1.6) 30/101	0.6 (0.3–1.2) 9/101	0.6 (0.3–1.1) 11/101

\* Age, smoking, and alcohol adjusted.

**Table 3. Risk of Laryngeal Cancer by Exposure Probability Levels and Anatomic Location of Tumor\***

Exposure Probability	All Cases	Supraglottic	Glottic	Others
	OR (95% CI) <i>n</i> <sub>cases</sub> / <i>n</i> <sub>controls</sub>			
Diesel exhaust				
Low	1.6 (1.2–2.2) 92/91	1.4 (0.9–2.1) 37/91	2.0 (1.2–3.2) 28/91	1.6 (1.0–2.6) 27/91
Medium	1.5 (1.1–1.9) 148/185	1.5 (1.1–2.0) 70/185	1.5 (1.0–2.3) 35/185	1.5 (1.0–2.1) 43/185

High	1.6 (1.1–2.4) 57/63	1.8 (1.1–2.9) 30/63	1.5 (0.8–2.9) 13/63	1.3 (0.7–2.5) 14/63
Gasoline exhaust				
Low	1.6 (1.1–2.2) 86/88	1.4 (1.0–2.2) 37/88	1.9 (1.2–3.1) 26/88	1.5 (0.9–2.5) 23/88
Medium	1.7 (1.3–2.2) 131/140	1.6 (1.1–2.2) 57/140	1.8 (1.1–2.7) 31/140	2.0 (1.3–2.9) 43/140
High	0.7 (0.2–2.9) 3/7	0.5 (0.1–4.3) 1/7	–	1.4 (0.3–7.3) 2/7
Polycyclic aromatic hydrocarbons				
Low	1.4 (1.0–1.8) 106/127	1.2 (0.8–1.8) 43/127	1.7 (1.1–2.8) 32/127	1.4 (0.9–2.1) 31/127
Medium	1.4 (1.1–1.7) 176/234	1.4 (1.1–1.9) 87/234	1.4 (0.9–2.0) 41/234	1.3 (0.9–1.8) 48/234
High	1.3 (1.0–1.7) 94/125	1.3 (0.9–1.9) 44/125	1.2 (0.7–1.9) 21/125	1.3 (0.8–2.1) 29/125
Formaldehyde				
Low	1.0 (0.7–1.4) 72/122	1.0 (0.6–1.5) 33/122	1.2 (0.7–2.1) 20/122	0.9 (0.6–1.5) 19/122
Medium	1.1 (0.6–2.2) 16/22	1.3 (0.6–3.0) 9/22	1.1 (0.4–3.2) 4/22	0.7 (0.2–2.3) 3/22
High	1.0 (0.1–11.2) 1/2	–	4.0 (0.3–47.7) 1/2	–
Solvent				
Low	0.7 (0.5–0.9) 83/196	0.6 (0.4–0.9) 36/196	0.7 (0.4–1.1) 20/196	0.7 (0.5–1.1) 27/196
Medium	1.1 (0.8–1.4) 131/203	1.2 (0.9–1.7) 70/203	0.9 (0.6–1.4) 26/203	1.0 (0.7–1.4) 35/203
High	0.7 (0.5–1.0) 57/132	0.8 (0.5–1.2) 30/132	0.6 (0.3–1.1) 12/132	0.6 (0.4–1.1) 15/132

\* Age, smoking, and alcohol adjusted.

Because we used JEM-based exposure assessment approach, study results carry the risk of misclassification. To test and eliminate possible misclassification coming from a low-level exposure probability group, we analyzed the risk of laryngeal cancer from diesel exhaust and gasoline exhaust exposures by separating low probability group from medium + high probability groups. Although we

observed excess risk in laryngeal cancers with both low probability - low intensity groups and medium + high probability - medium + high-intensity groups, excess risk in supraglottic cancers occurred with only medium + high probability - medium + high-intensity groups ([Table 4](#)).

**Table 4. Risk of Supraglottic Laryngeal Cancer by Diesel Exhaust and Gasoline Exhaust Intensity and Probability Levels\***

	Probability			
	All Cases		Supraglottic	
	Low OR (95% CI) <i>n</i> <sub>cases</sub> / <i>n</i> <sub>controls</sub>	Medium + High OR (95% CI) <i>n</i> <sub>cases</sub> / <i>n</i> <sub>controls</sub>	Low OR (95% CI) <i>n</i> <sub>cases</sub> / <i>n</i> <sub>controls</sub>	Medium + High OR (95% CI) <i>n</i> <sub>cases</sub> / <i>n</i> <sub>controls</sub>
Diesel Exhaust Exposure Intensity				
Low	1.6 (1.2–2.2) 88/87	1.3 (0.9–1.8) 73/98	1.5 (0.9–2.2) 37/87	1.0 (0.7–1.6) 27/98
Medium + High	2.0 (0.5–8.5) 4/4	1.6 (1.2–2.1) 132/150	–	1.9 (1.4–2.7) 73/150
Gasoline exhaust exposure Intensity				
Low	1.6 (1.1–2.2) 85/88	1.5 (1.0–2.2) 56/66	1.4 (0.9–2.2) 37/88	1.2 (0.7–1.9) 20/66
Medium + High	–	1.8 (1.3–2.5) 78/81	–	1.8 (1.2–2.8) 38/81

\* Age, smoking, and alcohol adjusted.

We were concerned about possible under adjustment for smoking when using ever/never classification. Analyses of the risk of laryngeal cancer from occupational exposures adjusted for quantitative data on smoking (pack-years) and ever/never alcohol showed that the exposure-response relationship between all laryngeal cancer sites and supraglottic cancer and exposure to diesel and gasoline exhaust still remained ([Table 5](#)).

**Table 5. Effects of Quantitative Smoking Data on the Risk of Laryngeal and Supraglottic Cancers**

Exposure intensity	All cases	Supraglottic
	OR (95% CI)* <i>n</i> <sub>cases</sub> / <i>n</i> <sub>controls</sub>	OR (95% CI)* <i>n</i> <sub>cases</sub> / <i>n</i> <sub>controls</sub>
Diesel exhaust		
Low	1.6 (1.1–2.3) 79/63	1.4 (0.8–2.3) 34/63
Medium + High	1.7 (1.1–2.6)	2.1 (1.3–3.4)

	67/45	41/45
$\chi^2$ for trend	14.5 ( $P < 0.001$ )	15.5 ( $P < 0.001$ )
Gasoline exhaust		
Low	1.6 (1.1–2.4)	1.5 (0.9–2.5)
	69/49	32/49
Medium + High	1.9 (1.1–3.2)	2.3 (1.2–4.2)
	47/27	25/27
$\chi^2$ for trend	12.8 ( $P < 0.001$ )	12.4 ( $P < 0.001$ )

\* Age, smoking pack year, and ever/never alcohol adjusted.

## Discussion

In the previous report, we identified several occupations such as production supervisors, textile workers, and drivers with increased risk of laryngeal cancer, especially supraglottic tumors. [14] We also found an elevated risk of laryngeal cancer with silica and cotton dust exposure. [15] In this report, we further evaluated the risk of laryngeal cancer with other occupational exposures including diesel exhaust, gasoline exhaust, PAHs, formaldehyde, and solvent exposures. We found an excess risk of laryngeal cancer with diesel exhaust, gasoline exhaust, and PAHs exposures, particularly for supraglottic cancers. The observed excess risk with PAHs appeared to be largely due to the association with diesel exposure since PAH-exposed workers without diesel exposure did not experience an elevated risk of laryngeal cancer.

A dose-response trend between diesel exhaust exposure and supraglottic tumors showed a twofold risk in the high intensity and probability groups. Diesel exhaust is a suspected lung carcinogen and pre-cancerous laryngeal papilloma has also been observed in hamsters exposed to diesel exhaust. [23] [24] Mutagenic effects of irritant components of diesel exhaust including carbon, sulfur, zinc, phosphorus, chromium and others may also play a role in the etiology of laryngeal cancer as well as other cancers. [8] [25] [26] Laryngeal cancer has been reported in diesel exhaust in some studies, [7] [10] [27] but not in others. [28] [29] Although we observed an excess risk with diesel exhaust exposure, we do not know which component might play an important role in development of laryngeal cancers.

We also observed an elevated risk among workers with potential exposure to gasoline exhaust. Carcinogenic effects of gasoline and gasoline vapors [17] [30] and its irritant effect on the supraglottic region has been previously reported. [31] Some studies considered diesel and gasoline exposures together and reported increasing risk of laryngeal cancer. [7] [10] An elevated incidence of laryngeal cancer was reported among benzene-exposed gasoline workers in Nordic countries. [32]

PAHs were the most prevalent exposure in this study group and we observed an excess risk of supraglottic laryngeal cancer with this exposure. Previous studies also showed increased risk of laryngeal cancer with PAHs exposure. [4] [33] [34] [35] However, we observed no excess among workers exposed to PAHs without suspected exposure to diesel exhaust, which suggests that the observed excess risk from PAHs might be caused by diesel exhaust exposure.

Chemicals, including formaldehyde, may cause irritation, inflammation, and metaplastic changes in the glottic area. [36] Some studies reported limited carcinogenic effects of formaldehyde and solvent exposure [37] [38] [39] [40] on laryngeal and nasopharyngeal carcinogenicity, [16] [41] [42] but not both. [43] [44] [45] [46] We, however, observed no association between formaldehyde or solvent exposure and laryngeal cancer risk.

In this study we evaluated the role of selected occupational chemical exposures in the etiology of laryngeal cancer. Lack of information on duration of exposure, socioeconomic status (SES), and monitoring data for occupational exposures are limitations of this study. Confounding by SES is unlikely because cases and controls were selected from Social Security Hospital for working-class people with relatively homogenous SES. In JEM analysis, there is always a risk of exposure misclassification because no direct measures of exposure were available. We also did not have duration of exposure data and even though we had accurate expert evaluation, data were still prone to the risk of misclassification. Although cancer patients as a control have been effectively used in past studies, [47] the lack of population-based controls could still be considered as a limitation. However, using cancer patients as a control might diminish the chance of recall bias. We also had available a small set of controls without cancer and analyses using these as controls did not show any significant differences from ORs based on cancer controls. Since the quantitative data on alcohol and tobacco use was missing for most of the subjects we adjusted ORs by ever/never use of tobacco and alcohol, and this could leave residual confounding. However, adjusting our models for age, available quantitative smoking (pack-years), and ever/never alcohol use did not change ORs for laryngeal and supraglottic cancers with diesel exhaust and gasoline exhaust exposures and exposure-response gradients were still observed. Previous reports found few examples of significant confounding occupational cancer associations by tobacco use. [48] [49]

The major strength of our study was the large number of larynx cancer cases from a developing country where incidence rate of laryngeal cancer is almost double that of the world rate and where occupational exposures may be greater than in developed countries. Modified seven-digit SOC and SIC codes gave us a chance to examine occupations and industries more specifically to develop a more sensitive JEM. In summary, we found some evidence that diesel and gasoline exhausts may be related with laryngeal cancer risk particularly for supraglottic cancers where a dose-response relationship was observed.

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