Proposed Updates to:

Cobalt and Cobalt Compounds Cancer Inhalation Unit Risk Factors

Technical Support Document for Cancer Potency Factors Appendix B

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Prepared by the

Office of Environmental Health Hazard Assessment

This document summarizes the changes made to the Cobalt and Cobalt Compounds Cancer Inhalation Unit Risk Factors Technical Support Document for Cancer Potency Factors, released by The Office of Environmental Health Hazard Assessment (OEHHA) in October 2020. Additions to the document are indicated by underlined text, and deletions from the document are indicated by ~~strikethrough~~ text. Only changes to the document and associated supporting text are contained herein; unchanged text are not included and are denoted by a line of six bolded asterisks. Unchanged section headings containing underlined text in the original document are denoted in bold. The October 2020 version can be found on the OEHHA website.

COBALT AND COBALT COMPOUNDS

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Changes to page 1:

II. HEALTH ASSESSMENT VALUES

Cobalt metal and water-insoluble cobalt compounds

Unit Risk Factor	7.7×10^{-3} $(\mu g/m^3)^{-1}$
Inhalation Slope Factor	27 $(mg/kg\text{-}day)^{-1}$

Water-soluble cobalt compounds (normalized to cobalt content)[1]

Unit Risk Factor	~~8.6×10^{-4} $(\mu g/m^3)^{-1}$~~ 1.0×10^{-2} $(\mu g/m^3)^{-1}$
Inhalation Slope Factor	~~3.0 $(mg/kg\text{-}day)^{-1}$~~ 35 $(mg/kg\text{-}day)^{-1}$

III. CARCINOGENICITY

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Change to page 2:

~~The IUR for insoluble cobalt (i.e., cobalt metal) is ninefold greater than the IUR for soluble cobalt sulfate heptahydrate, when normalized to cobalt content.~~ Differences in cellular uptake between soluble and insoluble forms of cobalt ~~have been proposed as a reason for differences in cancer potency~~ appear to play a role in cobalt-inducing lung cell genotoxicity, which may extend to ~~differences in~~ carcinogenic potential (Smith et al. 2014). *In vitro* studies observed that insoluble cobalt nanoparticles interacted with proteins on the surface of cells and were readily taken up, resulting in a considerably greater intracellular concentration of cobalt ion (following release in lyosomal fluid) when compared to uptake of extracellular ions from soluble cobalt compounds (Ponti et al., 2009; Colognato et al., 2008). A similar mechanism for carcinogenic, insoluble nickel compounds has also been observed, in which insoluble Ni particles are phagocytized by cells with subsequent intracellular dissolution, whereupon the released Ni ions interact with chromatin causing DNA damage (Costa, 1991; Costa *et al.*, 1994). Soluble nickel

[1] This update to the October 2020 Cobalt and Cobalt Compounds Cancer Inhalation Unit Risk (IUR) Factors document was done to address a correction that was published in 2022 (Anonymous, 2022) stating that the exposure concentrations of cobalt sulfate in the text, tables, and figures in Bucher et al. (1999) should have been expressed as anhydrous cobalt sulfate, and not cobalt sulfate heptahydrate.

salts are taken up more slowly by cells (as Ni ions) and do not produce the intracellular concentrations that insoluble nickel particles can produce.

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NTP Carcinogenicity Bioassays

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Changes to page 11:

Cobalt sulfate heptahydrate

Groups of F-344/N rats and B6C3F$_1$ mice (50 group/sex/species) were exposed to 0, 0.3, 1.0 or 3.0 mg/m^3 cobalt sulfate heptahydrate aerosol via whole-body inhalation for 6.2 hrs/day, 5 days/week, for 105 weeks (NTP, 1998a; Bucher *et al.*, 1999)[2]. The MMAD, recorded monthly, was within the range of 1 to 3 µm. Generation of the aerosol particles to which the rodents were exposed resulted in formation of primarily cobalt sulfate hexahydrate, although it is expected that environmental exposures to hydrated cobalt sulfate would be ~~the~~ a mix of both the hexahydrate and heptahydrate forms. The heptahydrate reportedly does not dehydrate to the hexahydrate until a temperature of 41.5º C is reached. The daily exposures included the 6 hour exposure time at a uniform aerosol concentration plus the ramp-up time of 12 min (0.2 hour/day) to achieve 90% of the target concentration after the beginning of aerosol generation. The decay time to 10% of the target concentration at the end of the exposures was in the range of 11-13 min.

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[2] The exposure group concentrations (0, 0.3, 1.0 or 3.0 mg/m^3) in the tables and text of the NTP study were expressed as the cobalt sulfate anhydrous salt, and do not represent exposure concentrations expressed as cobalt sulfate heptahydrate (Anonymous, 2022). For consistency, the term "cobalt sulfate heptahydrate" will be used to describe the rodent exposures since the heptahydrate was the test compound.

Changes to page 13:

Table 4. Unadjusted tumor incidence in rats exposed to cobalt sulfate heptahydrate for two years (NTP, 1998a) a,b,c

Tumor type		Incidence by concentration				Statistical *p*-values for pairwise comparison with controls (*p*-value for trend in control column)			
	mg/m^3	0	0.3	1.0	3.0	0	0.3	1.0	3.0
Male rat									
Lung: Alveolar/bronchiolar adenoma		1/50	4/50	1/48	6/50	0.032	0.181	0.742	0.056
Lung: Alveolar/bronchiolar carcinoma		0/50	0/50	3/48	1/50	0.233	1.000	0.114	0.500
Lung: Alveolar/bronchiolar adenoma or carcinoma		1/50	4/50	4/48	7/50*	0.023	0.181	0.168	0.030
Adrenal medulla: Benign pheochromocytoma[dc]		*14/50*	*19/50*	*23/49**	*20/50*	*0.193*	*0.198*	*0.041*	*0.146*
Adrenal medulla: Benign, complex or malignant pheochromocytoma		*15/50*	*19/50*	*25/49**	*20/50*	*0.239*	*0.263*	*0.027*	*0.201*
Adrenal medulla: Benign bilateral pheochromocytoma		*1/50*	*4/50*	*6/49*	*5/50*	*0.133*	*0.181*	*0.053*	*0.102*
Female Rat									
Lung: Alveolar/bronchiolar adenoma		0/50‡	1/49	10/50**	9/50**	<0.001	0.495	<0.001	0.001
Lung: Alveolar/bronchiolar carcinoma		0/50	2/49	6/50*	6/50*	0.012	0.242	0.013	0.013
Lung: Alveolar/bronchiolar adenoma, carcinoma, or squamous cell carcinoma		0/50‡	3/49	16/50**	16/50**	<0.001	0.117	<0.001	<0.001
Adrenal medulla: Benign pheochromocytoma		2/48‡	1/49	3/50	8/48*	0.002	0.492	0.520	0.045
Adrenal medulla: Benign, complex or malignant pheochromocytoma		2/48‡	1/49	4/50	10/48*	<0.001	0.492	0.359	0.014

(a) Exposure concentrations in the table are expressed as anhydrous cobalt sulfate (Anonymous, 2022).

~~(a)~~(b) The numerator represents the number of tumor-bearing animals; the denominator represents number of animals examined. Tumor type and incidence data in italics represents equivocal finding for carcinogenicity by NTP (1998a).

~~(b)~~(c) * = $p < 0.05$, ** = $p < 0.01$; *p*-value indicators are from pairwise comparisons with controls using Fisher exact tests performed by OEHHA. = $p < 0.05$, ‡ = $p < 0.01$, *p*-value indicators for trend in control incidence column determined using Cochran-Armitage trend test performed by OEHHA; numerical *p*-values for trend are in the statistical *p*-value control column.

~~(c)~~(d) Includes benign bilateral pheochromocytoma.

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Changes to page 15:

Table 5. Unadjusted tumor incidence in mice exposed to cobalt sulfate heptahydrate for two years (NTP, 1998a)[a,b,c]

Tumor type		Incidence by concentration				Statistical *p*-values for pairwise comparison with controls (*p*-value for trend in control column)			
	mg/m^3	0	0.3	1.0	3.0	0	0.3	1.0	3.0
Male mouse									
Lung: Alveolar/bronchiolar adenoma		9/50	12/50	13/50	18/50*	0.021	0.312	0.235	0.035
Lung: Alveolar/bronchiolar carcinoma		4/50	5/50	7/50	11/50*	0.014	0.500	0.262	0.045
Lung: Alveolar/bronchiolar adenoma or carcinoma		11/50‡	14/50	19/50	28/50**	<0.001	0.322	0.063	<0.001
Liver: Hemangiosarcoma		*2/50*	*4/50*	*8/50**	*7/50*	*0.066*	*0.339*	*0.046*	*0.080*
Female mouse									
Lung: Alveolar/bronchiolar adenoma		3/50	6/50	9/50	10/50*	0.031	0.243	0.061	0.036
Lung: Alveolar/bronchiolar carcinoma		1/50‡	1/50	4/50	9/50**	<0.001	0.753	0.181	0.008
Lung: Alveolar/bronchiolar adenoma or carcinoma		4/50‡	7/50	13/50*	18/50**	<0.001	0.262	0.016	<0.001
Liver: Hemangiosarcoma		*1/50*	*0/50*	*3/50*	*0/50*	0.713	0.50	0.308	1.000

(a) Exposure concentrations in the table are expressed as anhydrous cobalt sulfate (Anonymous, 2022).

~~(a)~~(b) The numerator represents the number of tumor-bearing animals; the denominator represents number of animals examined. Tumor type and incidence data in italics represents equivocal finding for carcinogenicity by NTP (1998a).

~~(b)~~(c) * = p<0.05, ** = p<0.01; p-value indicators are from pairwise comparisons with controls using Fisher exact test performed by OEHHA. = p<0.05, ‡ = p<0.001, p-value indicators for trend in control incidence column determined using Cochran-Armitage trend test performed by OEHHA; numerical p-values for trend are in the statistical p-value control column.

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IV. CANCER HAZARD EVALUATION

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Changes to pages 49 and 50:

Release of the cobalt ion in physiological fluids following inhalation is considered the primary factor for cancer risk. To compare cancer potencies of cobalt metal and cobalt sulfate heptahydrate, the exposure levels in the studies were calculated based on cobalt content alone. Thus, chamber concentrations of cobalt sulfate heptahydrate were normalized to the cobalt content. Since the exposure concentrations were expressed as the anhydrous cobalt sulfate in the tables and text of the ~~rodents in the~~ NTP study ~~were actually exposed to the hexahydrate~~ (Anonymous, 2022), the ~~hydrated cobalt sulfate chamber~~ concentrations of 0, 0.3, 1.0 and 3.0 mg/m^3 $CoSO_4$~~$\bullet 6H_2O$~~ were normalized to 0, 0.114 ~~067~~, 0.38 ~~22~~ and 1.14 ~~0.67~~ mg/m^3 Co, respectively (Behl *et al.*, 2015). Thus, it might be expected that the lowest concentration of cobalt metal (1.25 mg Co/m^3 ~~Co~~) would produce an equal, or greater, incidence of tumors than the highest concentration of ~~hydrated~~ cobalt sulfate normalized to cobalt content (1.14 ~~0.67~~ mg Co/m^3 ~~Co~~).

Comparing the two sets of NTP studies in this way, cobalt metal exposure at the lowest concentration (1.25 mg Co/m^3 ~~Co~~) produced a greater incidence of pulmonary tumors in the mice and male rats, and proportionally more pulmonary carcinomas than adenomas, compared to the highest concentration of ~~hydrated~~ cobalt sulfate (1.14 ~~0.67~~ mg Co/m^3 ~~Co~~). In female rats, exposure to cobalt metal at the lowest concentration produced a similar incidence of pulmonary tumors compared to the highest concentration of cobalt sulfate hexahydrate.

Also in the lung, the rare chemically-induced squamous cell neoplasms (predominantly CKE neoplasms) were found only in rats exposed to cobalt metal. Pancreatic islet tumors in male rats were observed only with exposure to cobalt metal, although at comparatively higher Co concentrations (2.5 and 5 mg/m^3) than those used in the cobalt sulfate heptahydrate studies. In addition, an increased incidence of mononuclear cell leukemia in female rats was observed only with exposure to cobalt metal. On the other hand, cobalt sulfate heptahydrate in rats at the highest exposure (1.14 ~~0.67~~ mg Co/m^3~~Co~~) produced approximately the same number of benign, malignant and benign/complex/malignant pheochromocytomas (combined) as that produced by cobalt metal at the lowest exposure concentration (1.25 mg Co/m^3).

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Changes to page 51:

Several epidemiology studies have been conducted, but were too limited or inadequate to assess the carcinogenic risk of cobalt in humans. A recent retrospective study by Sauni *et al*. (2017) did not find an increased total cancer risk or lung cancer incidence among 995 workers exposed to cobalt metal powder and cobalt compounds. However, respiratory protection was available to the workers (the level of use was not specified), and the young age and short exposure period for some of the workers may preclude an observed increase in cancer. In a direct comparison (i.e., without adjustment parameters such as inhalation rate and body weight), the highest cobalt levels the workers were exposed to (0.06 to 0.10 mg/m^3) were below the lowest cobalt sulfate heptahydrate concentration, <u>normalized to the content of cobalt</u> (0.114~~0.3~~ mg <u>Co</u>/m^3 ~~Co~~), used in the NTP rodent studies. This was a concentration that did not result in a measurable increase in tumor incidence in the rodents.

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V. QUANTITATIVE CANCER RISK ASSESSMENT

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<u>Cobalt Sulfate Heptahydrate</u>

<u>Effective tumor incidences</u>

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Changes to page 66 (table footnotes):

Table 12. Effective tumor incidence in rats exposed to cobalt sulfate heptahydrate for two years (NTP, 1998a)[a,b]

Tumor type		Incidence by concentration[c]				Statistical *p*-values for pairwise comparison with controls (*p*-value for trend in control column)			
	mg/m^3	0	0.3	1.0	3.0	0	0.3	1.0	3.0
Male rat									
Lung: Alveolar/bronchiolar adenoma		1/43	4/44	1/43	6/40*	0.022	0.187	0.753	0.044
Lung: Alveolar/bronchiolar carcinoma		0/24	0/28	3/34	1/25	0.209	1.000	0.194	0.510
Lung: Alveolar/bronchiolar adenoma or carcinoma		1/43	4/44	4/43	7/40*	0.014	0.187	0.180	0.022
Female Rat									
Lung: Alveolar/bronchiolar adenoma		0/39‡	1/33	10/37**	9/35**	<0.001	0.458	<0.001	<0.001
Lung: Alveolar/bronchiolar carcinoma		0/44	2/41	6/42*	6/46*	0.017	0.230	0.011	0.015
Lung: Alveolar/bronchiolar adenoma, carcinoma, or squamous cell carcinoma		0/44‡	3/41	16/42**	16/46**	<0.001	0.108	<0.001	<0.001
Adrenal medulla: Benign pheochromocytoma		2/39‡	1/37	3/38	8/38*	0.002	0.520	0.487	0.039
Adrenal medulla: Benign, complex or malignant pheochromocytoma		2/39‡	1/37	4/38	10/39	<0.001	0.520	0.325	0.012

(a) Exposure concentrations in the table are expressed as anhydrous cobalt sulfate (Anonymous, 2022).

(b) * = p < 0.05, ** = p < 0.001; p-value indicators are from pairwise comparisons with controls using Fisher exact tests performed by OEHHA. † = p < 0.05, ‡ = p < 0.01, p-value indicators for trend in control incidence column determined using Cochran-Armitage trend test performed by OEHHA; numerical p-values for trend are in the statistical p-value control column

~~(a)~~(c) The numerator represents the number of tumor-bearing animals; the denominator represents number of animals alive at the time of first occurrence of the tumor.

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Changes to page 67 (table footnotes):

Table 13. Effective tumor incidence in mice exposed to cobalt sulfate heptahydrate for two years (NTP, 1998a)[a,b]

Tumor type		Incidence by concentration[c]				Statistical *p*-values for pairwise comparison with controls (*p*-value for trend in control column)			
	mg/m^3	0	0.3	1.0	3.0	0	0.3	1.0	3.0
Male mouse									
Lung: Alveolar/bronchiolar adenoma		9/49	12/50	13/49	18/48*	0.016	0.331	0.234	0.030
Lung: Alveolar/bronchiolar carcinoma		4/50	5/50	7/49	11/48*	0.010	0.500	0.251	0.037
Lung: Alveolar/bronchiolar adenoma or carcinoma		11/50‡	14/50	19/49	28/48**	<0.001	0.322	0.055	<0.001
Female mouse									
Lung: Alveolar/bronchiolar adenoma		3/40	6/47	9/42	10/39*	0.015	0.330	0.069	0.029
Lung: Alveolar/bronchiolar carcinoma		1/49‡	1/49	4/49	9/45**	0.001	0.753	0.181	0.006
Lung: Alveolar/bronchiolar adenoma or carcinoma		4/49‡	7/49	13/49*	18/45*	<0.001	0.262	0.015	<0.001

(a) Exposure concentrations in the table are expressed as anhydrous cobalt sulfate (Anonymous, 2022).

(b) * = $p < 0.05$, ** = $p < 0.01$; p-value indicators are from pairwise comparisons with controls using Fisher exact test performed by OEHHA. = $p < 0.05$, ‡ = $p < 0.01$, *p*-value indicators for trend in control incidence column determined using Cochran-Armitage trend test performed by OEHHA; numerical *p*-values for trend are in the statistical *p*-value control column.

~~(a)~~(c) The numerator represents the number of tumor-bearing animals; the denominator represents number of animals alive at the time of first occurrence of the tumor.

Changes to page 68:

Calculation of single- and multi-site tumor cancer slope factors

For the derivation of the CSF, cobalt sulfate heptahydrate ~~chamber concentrations~~ expressed in the anhydrous ~~form in~~ concentrations of 0, 0.3, 1.0 and 3.0 mg/m^3 were time-adjusted (6.2 hours/24 hours x 5 days/7 days) to extrapolate from the intermittent lab exposure conditions to a continuous exposure over the life span of the animals (*i.e.*, to simulate an annualized average air concentration). The time-adjusted cobalt sulfate heptahydrate concentrations of 0, 0.055, 0.18, and 0.55 mg/m^3 were used to calculate the average daily dose in mg/kg BW-day.

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Table 14. Calculated average daily exposed dose (mg/kg-day) of cobalt sulfate heptahydrate, expressed as the anhydrous salt, in the rats and mice during the two-year exposures (rounded to two significant figures in the final assessment)

Species and Sex	Cobalt Sulfate ~~$SO_4 \cdot 7H_2O$ Chamber~~ Concentration (mg/m^3)			
	0	0.3	1.0	3.0
	Daily Exposed Dose (mg/kg-day)			
Rats				
Males	0	0.051	0.17	0.51
Females	0	0.061	0.20	0.61
Mice				
Males	0	0.064	0.21	0.64
Females	0	0.065	0.22	0.65

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Changes to page 70:

Comparison of the single-site and multi-site human CSFs in Table 15 shows the CSF_h of 13.41 (mg/kg-day)$^{-1}$ based on the female rat multi-site tumor data to be the most sensitive indicator of cancer risk for cobalt sulfate heptahydrate. Since the cobalt ion is considered to be the primary factor for cancer risk, the anhydrous cobalt sulfate ~~heptahydrate~~ CSF is normalized to the content of cobalt. ~~As discussed in Section III, generation of the aerosol particles to which the rodents were exposed resulted in formation of primarily cobalt sulfate hexahydrate, although it is expected that environmental exposures to hydrated cobalt sulfate would be to the heptahydrate form.~~

~~Thus~~ Therefore, the molecular weight of cobalt is divided by the molecular weight of anhydrous cobalt sulfate ~~hexahydrate~~ (58.93 Co / 154.996 ~~263.1~~ $CoSO_4$ ~~• $7H_2O$~~ = 0.3802 ~~0.2239~~) to calculate the molecular weight fraction of cobalt in anhydrous cobalt sulfate. The CSF_h of 13.41 $(mg/kg\text{-}day)^{-1}$ is then ~~and multiplied~~ divided by ~~13.41 $(mg/kg\text{-}day)^{-1}$~~ 0.3802 to ~~result in an~~ calculate the adjusted CSF of ~~3.0~~ 35.27 $(mg\ Co/kg\text{-}day)^{-1}$, which is rounded to 35 $(mg\ Co/kg\text{-}day)^{-1}$ in the final assessment.[3]

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Changes to page 72:

Calculation of inhalation unit risk

The Inhalation Unit Risk (IUR) describes the excess cancer risk associated with an inhalation exposure to a concentration of 1 $\mu g/m^3$ and is derived from the cobalt sulfate heptahydrate CSF. ~~Using a~~ Appling the human breathing rate of 20 m^3/day, an average human BW of 70 kg, and a mg-to-µg conversion factor of 1,000 as shown in Eq. 6-4, the IUR was calculated ~~as shown in Eq. 6-4 (see above)~~ to be 0.010 $(\mu g\ Co/m^3)^{-1}$ or 1.0×10^{-2} $(\mu g\ Co/m^3)^{-1}$.

~~Using the cobalt-normalized CSF of 3.0 $(mg\ Co/kg\text{-}day)^{-1}$ results in a calculated IUR of 0.00086 $(\mu g\ Co/m^3)^{-1}$ or 8.6×10^{-4} $(\mu g\ Co/m^3)^{-1}$.~~ Thus, the extra cancer risk associated with continuous lifetime adult exposure to 1 $\mu g/m^3$ cobalt sulfate heptahydrate normalized to the cobalt content is ~~8.6~~ 100 in ~~ten thousand~~ 10,000, or ~~860~~ 10,000 in ~~a~~ 1 million.

VI. CONCLUSIONS

Carcinogenicity studies conducted by NTP established clear evidence of carcinogenicity for cobalt metal and cobalt sulfate heptahydrate. Release of the cobalt ion in physiological fluids is considered the primary factor for cancer risk. The lungs were the primary site of tumor formation in both rats and mice, and both cobalt metal and cobalt sulfate heptahydrate induced tumors of the same histogenic type in lungs. Cobalt metal and cobalt sulfate heptahydrate exposure also induced tumors at multiple sites in rats. Carcinogens that produce tumors in more than one species have the greatest potential to induce tumors in other species, including humans. For each cobalt compound, the CSF was based on the most sensitive species and sex. Derivation of an IUR for cobalt metal (7.7×10^{-3} $(\mu g/m^3)^{-1}$) is based on lung tumor formation in male mice. The IUR

[3] The same CSF of 35 $(mg\ Co/kg\text{-}day)^{-1}$ was also calculated when starting with exposure concentrations normalized to cobalt content of 0, 0.114, 0.38, and 1.14 mg Co/m^3.

derivation for cobalt sulfate heptahydrate, normalized to cobalt content (~~8.6~~ 1.0 × 10^{-4}~~^{2}~~ (μg Co/m^3)$^{-1}$), is based on a multi-site analysis of lung and adrenal medulla tumors observed in female rats.

Change to page 73 (addition of reference):

VII. REFERENCES

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Anonymous (2022). Correction to: Inhalation toxicology and carcinogenicity studies of cobalt sulfate. Toxicol Sci 188(2): 276.

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