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**COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD,
CONSUMER PRODUCTS AND THE ENVIRONMENT**

IPCS Mode of Action Human Relevance Framework (HRF)

1) The International Programme on Chemical Safety (IPCS) Mode of Action (MOA) Framework is a conceptual framework for considering data on the mode of action of chemical carcinogens. It is intended to be used by regulators as part of the hazard assessment process as an analytical tool to provide a means of evaluating systematically the data available on the mode of action of a specific carcinogenic response to a chemical in a transparent way. The COC considered aspects of the Framework in 1999 and in 2004, considering in detail the Human Relevance Framework (HRF) developed by a working group sponsored by the US Environmental Protection Agency and the International Life Science Institute (ILSI) Risk Science Institute (RSI). The HRF extends the MOA approach by considering whether the key events in the MOA are plausible in humans. The COC considered that the MOA and HRF approaches both provided a logical framework in which to set the information needed when assessing the relevance of chemical induced animal tumours to humans.

2) During the horizon scanning exercise in 2006 and 2007, members agreed that the committee should review the IPCS MOA Framework again when the updated version, including a HRF and case studies, was published. The relevant papers were published in *Critical Reviews in Toxicology* in late 2006. In the first paper by Boobis et al. (2006) the IPCS updates its 2001 MOA framework based on experience gained since 2001 and they also took into consideration the 2003 ILSI/RSI human cancer relevance framework in producing a unified Human Cancer Relevance Framework (IPCS HRF). The three case studies provide worked examples of the IPCS HRF, illustrating a rigorous and transparent approach for determining the sufficiency of evidence and the relevance of an animal MOA for humans (Cohen et al., 2006; McGregor et al., 2006 and Dellarco et al., 2006). The papers are attached in Annex A.

IPCS Framework for Analyzing the Relevance of a Cancer Mode of Action for Humans (Boobis *et al.*, 2006).

3) This paper updates the Mode of Action Framework document published by the IPCS (WHO/ILO/UNEP) in 2001 and extends the MOA framework to consider human relevance. This paper outlines the role of the IPCS in developing the HRF framework and details the 2001 IPCS conceptual MOA framework and the updates made to the framework guidelines for evaluating animal carcinogenesis. The paper describes the updated version of the

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animal MOA Framework, which is based on the Bradford Hill criteria, and details each section individually (1) Postulated mode of action, 2) Key events, 3) Concordance of dose-response relationship, 4) Temporal association, 5) Strength, consistency and specificity of association of tumour response with key events 6) Biological plausibility and coherence 7) Other modes of action 8) Uncertainties, inconsistencies and data gaps and 9) Assessment of postulated mode of action.

4) The development of the IPCS MOA framework to address human relevance (IPCS HRF) used the IPCS MOA framework and the ILSI/RSI HRF as a basis for this activity. The resulting IPCS HRF involves answering a series of 3 questions followed by a conclusion regarding the human relevance of the MOA underlying animal tumours. The application of the guidance results in a narrative with four sections that can be incorporated into the hazard characterisation of a risk assessment.

The four sections are:

- I. Is the weight of evidence sufficient to establish a MOA in animals?
- II. Can human relevance of the MOA be reasonably excluded on the basis of fundamental, qualitative differences in key events between experimental animals and humans?
- III. Can human relevance of the MOA be reasonably excluded on the basis of fundamental, quantitative differences in key events between experimental animals and humans?
- IV. Statement of confidence, analysis and implications

5) Section 1 requires the application of the updated IPCS MOA framework. Section 2 represents a qualitative assessment of the relevance of the MOA to human cancer potential. For purposes of human relevance analysis, if the MOA in experimental animals is judged to be qualitatively relevant to humans, section 3 represents a more quantitative assessment that takes into account any kinetic and dynamic information that is available from both the experimental animals and humans. The committee should note that the wording of section 2 and 3 of the IPCS/HRF differs from the ILSI/RSI framework on the implications of a “yes” or “no” answer to the original question. The questions were changed to enable a yes/no answer, but qualified by the descriptor “reasonably”, based on the recognition that decisions about the adequacy of “weight of evidence” are not absolute but involve scientific judgement based on transparent analysis of available data. Section 4 is the final section of the analysis and includes a statement of confidence in the quality and quantity of data underlying the analysis, consistency of the database and the nature and extent of the concordance analysis. Details of the mode of action and specific data gaps which were identified are also included in this section.

6) In order to assist dissemination of the framework the paper suggests the generation of a database which would include accepted modes of action and their associated key events. The paper also discusses the application of the IPCS HRF to DNA-reactive carcinogens. Similarities exist in the carcinogenic

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process between rodents and humans and the comparable interactions with DNA by DNA-reactive carcinogens. It is reported that it would be expected that in general, DNA-reactive carcinogens would progress to section 2, answering “no” to the question –“Can human relevance of the MOA be reasonably excluded on the basis of fundamental, qualitative differences in key events between experimental animals and humans?”. It is also thought that the IPCS HRF can also assist in quantifying differences in key events between rodents and animals that may be of value in extrapolating risk to humans. The paper discusses the role of the IPCS HRF in risk assessment, with the strengths of the framework and its application to provide information to the risk characterisation step of the risk assessment process outlined in the paper.

7) The paper concludes with a number of general points including the need for careful evaluation of the weight of evidence for a carcinogenic response in experimental animals, the need for involvement of scientists in the development, acceptance and review of a novel MOA, the applicability of the Framework to all MOAs for carcinogens, the use of the human relevance analysis as a valuable approach to enhance understanding and risk characterisation, the importance of considering potentially susceptible subgroups and different life stages in the analysis and the development of a database of generally accepted MOAs and informative cases. There is also the need for focused analysis when the MOA is novel and a detailed evaluation via the HRF is required. However, when a chemical produces a tumour response consistent with an already established MOA, the analysis is more focused on the established MOA and a determination of whether the chemical produces its carcinogenic effect via the same key events established for the pathway. The need to consider rigorously alternative modes of action, before accepting a specific MOA as causative of a carcinogenic response, is emphasised.

8) The following paragraphs of this overview paper detail three case studies that use the IPCS HRF as an approach for determining the sufficiency of evidence and the relevance of an animal MOA for humans.

Thiazopyr and Thyroid disruption: Case study within the context of the 2006 IPCS Human Relevance Framework for analysis of a Cancer Mode of Action (Dellarco *et al.*, 2006).

9) Thiazopyr is a non-DNA reactive herbicide that induces rat thyroid-follicular cell tumours. This agent formed the case-study used in the 2001 IPCS MOA analysis. It is revisited in this paper to illustrate the additional guidance provided in the 2006 IPCS HRF. The paper provides a brief summary of the available carcinogenicity data for thiazopyr, where thiazopyr has been found to induce thyroid tumours only in male rats and appears to do so by increasing the hepatic metabolism and clearance of thyroid hormones. The postulated MOA involves perturbation of homeostasis of the pituitary-thyroid axis by an extra-thyroidal mechanism. The key events identified in the thiazopyr MOA are

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- Induction of hepatic UGT activity
- Increase in hepatic metabolism and biliary excretion of thyroxin
- Decrease in serum thyroxin half life and concentration
- Increase in circulating thyroid-stimulating hormone (TSH) concentration
- Cellular thyroid hypertrophy and follicular-cell hyperplasia

10) The paper details dose response relationship analyses, concordance and temporal analyses for the key events. Dose-response studies which investigate effects on the liver, hormones and thyroid (key areas of thiazopyr mode of action) are analysed. Effects such as increased hepatic thyroxin-UGT activity, increased clearance of thyroxin from the blood and elimination in bile, decreases in thyroxin serum level, increases in TSH levels, increases in absolute liver weights, increases in incidence of liver hypertrophy were all observed in key studies (Hotz et al., 1997; Naylor and McDonald, 2002). In order for an event to be an essential element of the tumorigenic response, the event must precede tumour appearance. The paper provides evidence that shows that there is a logical temporal relationship for the key events in thiazopyr-induced thyroid follicular-cell tumour formation, in which all key events precede tumour formation. The authors also establish strength, consistency and specificity of association of the tumour response with key events from the studies of Hotz et al. (1997) and Naylor and McDonald, (1992). From the evidence that was available in the literature, the authors were able to find biological plausibility and coherence in the data to support a relationship between sustained perturbation of the hypothalamic-pituitary-thyroid axis, prolonged stimulation of the thyroid gland by TSH and the progression of thyroid follicular cells to hypertrophy, hyperplasia and eventually neoplasia.

11) Other modes of action were also considered including mutagenesis. No genetic toxicity was evident in a number of test systems including *Salmonella Typhimurium* test, *hgpt* locus of CHO cells, MN induction in bone marrow of mice treated *in vivo* and UDS induction in hepatocytes treated *in vivo*, indicating that mutagenesis is not an alternative MOA. In the section on “uncertainties, inconsistencies and data gaps”, the authors indicated that there was a lack of dose concordance for thyroid tumours and hormone changes. Reasons given for the lack of dose concordance were inaccuracies in doses (mg/kg bw/d), which were either estimated and cover an early period in the life of rats or were averages for the whole duration of the experiment. The authors are confident that the assessment of the postulated MOA of thiazopyr is adequate to explain the development of thyroid follicular-cell tumours in rats following chronic dietary exposure to thiazopyr.

12) The IPCS HRF as outlined above (Boobis et al., 2006) is used to address a series of three questions and concludes with a documented statement regarding the human relevance of the MOA underlying rat thyroid follicular-cell tumours following exposure to thiazopyr. In response to question 1, the authors report clear evidence that thiazopyr alters thyroid homeostasis

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through the action of UGT in the liver, reducing serum thyroxin (T4) levels and consequently causing elevated serum TSH. In response to question 2, the authors conclude that the fundamental mechanisms involved in the function and regulation of the hypothalamic-pituitary-thyroid axis in rats are qualitatively similar to those in humans. In response to question 3, on the basis of studies on other compounds with the same MOA, the authors found substantial differences in the dose response relationship for altered homeostasis of the pituitary-thyroid axis in rats compared with humans and this indicates that there are differences in tumour susceptibility between rats and humans following exposure to thiazopyr. The differences are due to quantitative dynamic differences between rats and humans in the basic physiological and biochemical processes underlying pituitary-thyroid function. Differences include smaller reserve capacity of thyroid and shorter half-life of T4 in rats compared to humans. There is also increased clearance of T4 in rats, leading to higher rates of production of T4 (per unit body weight) to maintain normal levels of T4. The thyroid gland is also less active in humans. TSH levels are approx 25 times higher in rats than humans. Humans are quantitatively less sensitive than rats to agents that reduce T4 and lead to elevated TSH. Histological differences in the thyroid also exist between rats and humans. The histological difference is related to the higher rate of production of T4 in rats, thus making the rat thyroid more functionally active than humans. The follicular epithelium in rats is stimulated to synthesize thyroglobulin and therefore more of the cells are tall cuboidal and active in synthesis. In humans, the cells are short cuboidal and almost squamous in appearance, suggesting they are quiescent. This leads to differences in response of rat and human cells when they are stimulated by TSH.

13) There is clear evidence to establish that the MOA for thiazopyr-induced thyroid follicular-cell tumours in rats involves thyroid disruption. However, the authors conclude that it is not likely that exposure to thiazopyr will lead to an increase in susceptibility to this type of tumour development in humans. Substantial differences in basic physiological and biochemical processes between humans and rats lead the authors to conclude that exposure to thiazopyr will not result in thyroid perturbation and hence the development of thyroid tumours in humans.

Formaldehyde and Glutaraldehyde and Nasal Cytotoxicity: Case study with the context of the 2006 IPCS Human Framework for the analysis of a cancer mode of Action for humans (McGregor *et al.*, 2006).

14) Formaldehyde and glutaraldehyde are highly reactive aliphatic mono- and dialdehydes, respectively, and produce covalently cross-linked DNA-protein and protein-protein complexes. The paper provides a brief summary of the available carcinogenicity data on formaldehyde and glutaraldehyde, where inhalation studies have shown that formaldehyde induces nasal tumours in rats but no nasal tumours were observed in the only 2-year study of rats exposed to glutaraldehyde. The postulated MOA involves sustained cytotoxicity and cell proliferation following prolonged exposure above a critical concentration. Neoplasia occurs as a result of genetic changes within the

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proliferating cell population, with these changes postulated to be secondary to the cytotoxicity, metaplasia and hyperplasia. Although formaldehyde is genotoxic in vitro, the carcinogenic effect is more consistent with the postulated MOA, which involves sustained cytotoxicity. The key events identified in the postulated MOA for formaldehyde are:

- Cytotoxicity
- DNA-Protein crosslinks (DPX) formation
- Nasal epithelial cell regenerative proliferation
- Squamous metaplasia
- Inflammation

15) The paper details dose response relationship analyses, concordance and temporal analyses. A non-linear dose response pattern was observed for key events in rats exposed to formaldehyde. Effects such as increases in cell turnover, DNA synthesis, epithelial cell proliferation, DPX formation and squamous metaplasia in nasal turbinates were observed in a number of studies. Similarly, exposure to glutaraldehyde resulted in hyperplasia and squamous metaplasia on the lateral wall of the nasal cavity and on the tip of the nasal turbinates. Effects also noted were inflammation of the nasal cavity, cell proliferation in squamous epithelium of the nasal vestibule and exposure-related increase in cell replication (NTP, 1993). Following exposure to a concentration of formaldehyde of 2 ppm or higher, a sustained increase in cell proliferation (2-10 fold higher) of nasal epithelial cells is observed, irrespective of exposure period. Regenerative cell proliferation following formaldehyde-induced cytotoxicity increases the number of DNA replications and thus the probability of DNA replication errors resulting in mutations. However, the data relating to the temporal association for DPX are limited due to the short duration of the DPX studies (exposures of 1 day). For glutaraldehyde, a temporal relationship was observed between increased cell proliferation and metaplasia.

16) The paper reports good strength, consistency and specificity of association of tumour response with key events for formaldehyde. The proposed MOA for formaldehyde-induced nasal tumours in animals exposed by inhalation is consistent with biological plausibility and the available data (sustained cell proliferation and histopathological effects in the nasal cavity in a range of animal studies of varying duration). Cytotoxicity and cell proliferation have also been demonstrated with glutaraldehyde, however, this agent did not induce nasal tumours in rats or mice.

17) Other modes of action were also considered including mutagenesis. From the available data, formaldehyde is genotoxic in vitro but generally not genotoxic in standard in vivo tests; although there are many studies demonstrating that it produces DNA-protein cross links. Glutaraldehyde has been less extensively studied than formaldehyde for genotoxicity in vitro and in vivo. It produces weak and inconsistent positive findings in vitro and is not active in the majority of the in vivo studies. The authors conclude that if genotoxicity was the major mode of action for the carcinogenicity of formaldehyde, it remains to be explained why glutaraldehyde is not active.

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18) The paper discusses the uncertainties, inconsistencies and data gaps for formaldehyde and glutaraldehyde. There are only limited data available on intermediate endpoints such as proliferative responses as a measure of cytotoxicity and DPX. Inconsistencies also exist with regard to the base pair mutation found in the *hprt* mutation spectrum of formaldehyde. Glutaraldehyde has been shown to be more cytotoxic than formaldehyde, with primarily different nasal tissues affected following exposure to the two compounds. This difference in site of toxic action may be important and this data gap needs investigating. Using the IPCS HRF (Boobis et al., 2006) the authors address the three questions posed and conclude with a documented statement regarding the human relevance of the MOA underlying nasal tumours following exposure to formaldehyde. The authors consider that there is high confidence for the postulated MOA of formaldehyde, based on the weight of evidence, and that it is adequate to explain the development of nasal tumours in rats and mice following exposure to formaldehyde. For glutaraldehyde, similar key events have been demonstrated but it does not produce nasal tumours in rats and mice. If the proposed MOA for formaldehyde is to be maintained, an explanation for this discrepancy is necessary. A hypothesis has been proposed involving the dialdehyde function of glutaraldehyde. This function may inhibit the macromolecules such as proteins with which it reacts from further reaction within the cellular environment. Should these macromolecules be proteins involved in the maintenance of survival, then their immobility perhaps more likely leads to cell death than to a change in differentiation state. The immobilization of macromolecules by glutaraldehyde contributes to the very much higher toxicity of the dialdehyde. The monoaldehyde function of formaldehyde also causes cellular damage but proteins involved in cellular differentiation may be able to continue to function in that role, although with an altered outcome that may be the beginning of a path to neoplasia. Repair of alkylated nucleotides, following reaction of the aldehydes with nucleic acids, may be difficult or impossible in the case of glutaraldehyde, whereas repair will occur following formaldehyde interaction with DNA.

19) In response to question 2 of the IPCS HRF, cytotoxicity and cell proliferation are plausible in humans. There is also evidence of nasal tumours in humans following exposure to formaldehyde. For DPX formation, in humans, a positive association with exposure to formaldehyde has been observed in non target cells (peripheral lymphocytes) in exposed workers. For glutaraldehyde, cytotoxicity and cell proliferation are plausible in humans but there have been no studies of these effects following glutaraldehyde exposure in humans. There is no evidence that glutaraldehyde produces nasal tumours in humans, although studies are limited. In response to question 3 of the IPCS HRF, the authors reported that there were likely to be quantitative differences between animal species and humans due to differences in the dosimetry in the respiratory tract but that there do not appear to be fundamental differences that would indicate that the proposed MOA for formaldehyde is not relevant for humans. For glutaraldehyde, the

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paper indicates that there is much less known on the kinetics of glutaraldehyde than formaldehyde in experimental animals.

20) To address the statement of confidence, analysis and implications, the paper reports that there is clear evidence establishing a MOA involving cytotoxicity and cell proliferation for formaldehyde-induced nasal tumours in rats and mice and that this MOA is considered relevant to humans, despite limitations in the human data. For glutaraldehyde, the MOA proposed for formaldehyde would appear to be potentially relevant, but tumour formation has not been demonstrated, possibly due to the chemical nature of the respective aldehyde-macromolecule complexes.

4-Aminobiphenyl and DNA reactivity: Case study within the context of the 2006 IPCS Human Relevance Framework for analysis of a cancer mode of action for humans (Cohen et al., 2006).

21) 4-Aminobiphenyl is a DNA reactive carcinogen that induces urinary bladder cancer in individuals exposed to high levels occupationally and in cigarette smokers. The paper provides a summary of the available animal carcinogenicity data for 4-aminobiphenyl where 4-aminobiphenyl is primarily a carcinogen of the liver and to a lesser extent the urinary bladder in mice. In dogs (and humans), the urinary bladder is the target organ. The postulated MOA involves metabolism of 4-aminobiphenyl by hepatic enzymes to N-hydroxy-4-aminobiphenyl, which can be esterified (N-glucuronidated, N-sulfated, N-acetylated) in hepatic and other tissues. Ultimately, a reactive electrophilic nitrenium ion is formed in the target tissue following de-esterification and this is capable of forming DNA adducts. The principle DNA adduct is N-(deoxyguanosin-8-yl)-4-aminobiphenyl. As a result of the mutations that can result from these reactions at critical sites of critical genes, neoplastic cells eventually develop. The key events identified in the MOA for 4-aminobiphenyl are:

- Metabolic activation [(a) N-hydroxylation; (b) N-esterification; (c) hydrolysis to nitrenium ion]
- DNA adduct formation (dG-C8, dA-C8, dC-C8) in pluripotential cell of target organ
- DNA mutation in critical genes
- Cancer

22) Data on concordance of the dose response for precursor lesions for tumours are restricted to hyperplasia in the mouse bladder. The dose-response curves were sigmoidal or hockey-stick shaped. In contrast, steady-state levels of urothelial C-8 guanine DNA adducts showed linear dose response in mice, following chronic administration of 4-aminobiphenyl. The paper provides evidence that shows that there is a logical temporal relationship for the key events such as DNA adducts formation, in which they all precede tumour formation. The authors also establish strength, consistency and specificity of association of the tumour response with key events from a large number of studies. Evidence in support of the association

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of the tumour response with key events comes only in part from studies on bladder with considerable evidence provided from studies on liver. From the evidence that was available, such as DNA adduct formation and the fact that 4-aminobiphenyl is mutagenic in organs in which tumours develop, the authors were able to find biological plausibility and coherence in the data to support a relationship between exposure to 4-aminobiphenyl and cancer of the bladder and liver.

23) Alternative modes of action were considered. Other components of the already described modes of action including the role of hepatic enzymes other than CYP1A2 in producing the hydroxylated metabolite were also considered. These alternatives would affect either alternative specific aspects or associative processes that could affect quantitative aspects. Although the specific enzymes involved in the metabolic activation may vary, the sequence of generation of a reactive electrophile, DNA adduct formation, mutagenesis and carcinogenesis were considered to be consistent. Data gaps remain concerning details of the specific enzymes involved, the basis for differing organ specificity between species and details regarding potency, and the shape of the dose response curve in humans. These uncertainties need to be considered quantitatively in the overall assessment.

24) To address section 2 of the IPCS HRF, there is considerable evidence in humans (in individuals exposed to 4-aminobiphenyl in cigarette smoke) and human cell systems in support of each of the key events for 4-aminobiphenyl induced urinary bladder cancer. Furthermore, there is extensive epidemiological evidence demonstrating urinary bladder carcinogenicity in humans following exposure to 4-aminobiphenyl. In summary, the paper reports that on a qualitative basis, the key events in the mode of action are the same in dogs, mice and humans: metabolic activation to the N-hydroxylamine with subsequent formation of a reactive electrophile, formation of guanine adducts, gene mutation and formation of cancer.

25) To address section 3 of the IPCS HRF, the paper suggests that kinetic differences in absorption, distribution and metabolism are not significant between dogs, mice and humans based on the similarities in the levels of DNA adduct formation in the urothelium. Although similar enzymatic processes occur in the three species, quantitative differences are evident amongst the enzymes involved. The paper suggests that these differences may explain some of the variations seen in the target organ specificity among the species and might suggest possible quantitative differences in generation of the DNA adducts. However, these differences do not negate the overall mode of action for any of the species or the different target organs and are consistent with the complexity of the competing pathways for metabolic activation and deactivation. Quantitative differences in the potential to repair different adducts may also exist among species. Modulating factors have also been identified that can quantitatively affect the ultimate formation of the urothelial DNA adducts, such as pH and frequency of urination. No evidence implicating another mode of action was identified but significant quantitative differences exist between species with regard to apparent potency of 4-

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aminobiphenyl with respect to urinary bladder carcinogenesis. To address section 4 of the IPCS HRF, the authors conclude that there is clear evidence in the available data that the mode of action for 4-aminobiphenyl is well supported in the animal model. The MOA is also relevant to humans both qualitatively and quantitatively. Their overall conclusion, based on the evaluation, even without the epidemiological data, is that 4-aminobiphenyl poses a cancer hazard to humans.

26) In conclusion, the IPCS HRF provides a systematic approach for judging whether data support a postulated mode of carcinogenic action for a chemical and for evaluating its relevance to humans. It provides an effective structured means of identifying key data gaps, and hence in guiding the experimental plan, both prospectively and retrospectively. Even when human relevance cannot be dismissed, application of the framework provides insight into a number of aspects of the carcinogenic profile of the compound that can be carried forward into the remainder of the risk assessment. Such information can include the nature of the dose-response relationship, the existence of biological thresholds, the potential basis for interindividual differences in susceptibility and even possibly the interpretation of biomarkers.

Questions for the Committee:

- 1) What are the views of the Committee on the IPCS HRF?
- 2) Would the Committee wish to use this approach on an example such as oestrogens?
- 3) Does the Committee wish to be updated on developments in this field, such as the ongoing IPCS activity?

Secretariat, Feb 2008

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Annex A to CC/08/3

Critical Reviews in Toxicology, 36(10), pp 781-835.

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