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KARYA ILMIAH : JURNAL ILMIAH

Judul Artikel Ilmiah : Activation of interleukin-6 and -8 expressions by methylmercury in human U937 macrophages involves RelA and p50

Penulis Artikel Ilmiah : Megumi Yamamoto, Noureen Khan, **Muflihatul Muniroh**, Eriko Motomura, Rie Yanagisawa, Takami Matsuyama, Christoph F. A. Vogel

Status Pengusul : Penulis pertama/**penulis anggota**/penulis korespondensi

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- i. Terindeks di : SCOPUS (Q2); SJR 0,8

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Ruang Lingkup dan Kedalaman Pembahasan : Dalam introduction dapat dipahami kepentingan melakukan penelitian ini, dan urgency serta manfaatnya. Namun general informasi mengenai Minamata disease tidak diuraikan sehingga awam akan mengalami kesulitan.

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Nilai Total = (100%)	40			37
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KOMENTAR/ULASAN PEER REVIEW


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Ruang Lingkup dan Kedalaman Pembahasan : Pembahasan dijelaskan secara mendalam, menampilkan gambar-gambar pendukung dan telah mencitasi hampir semua jurnal <10 tahun

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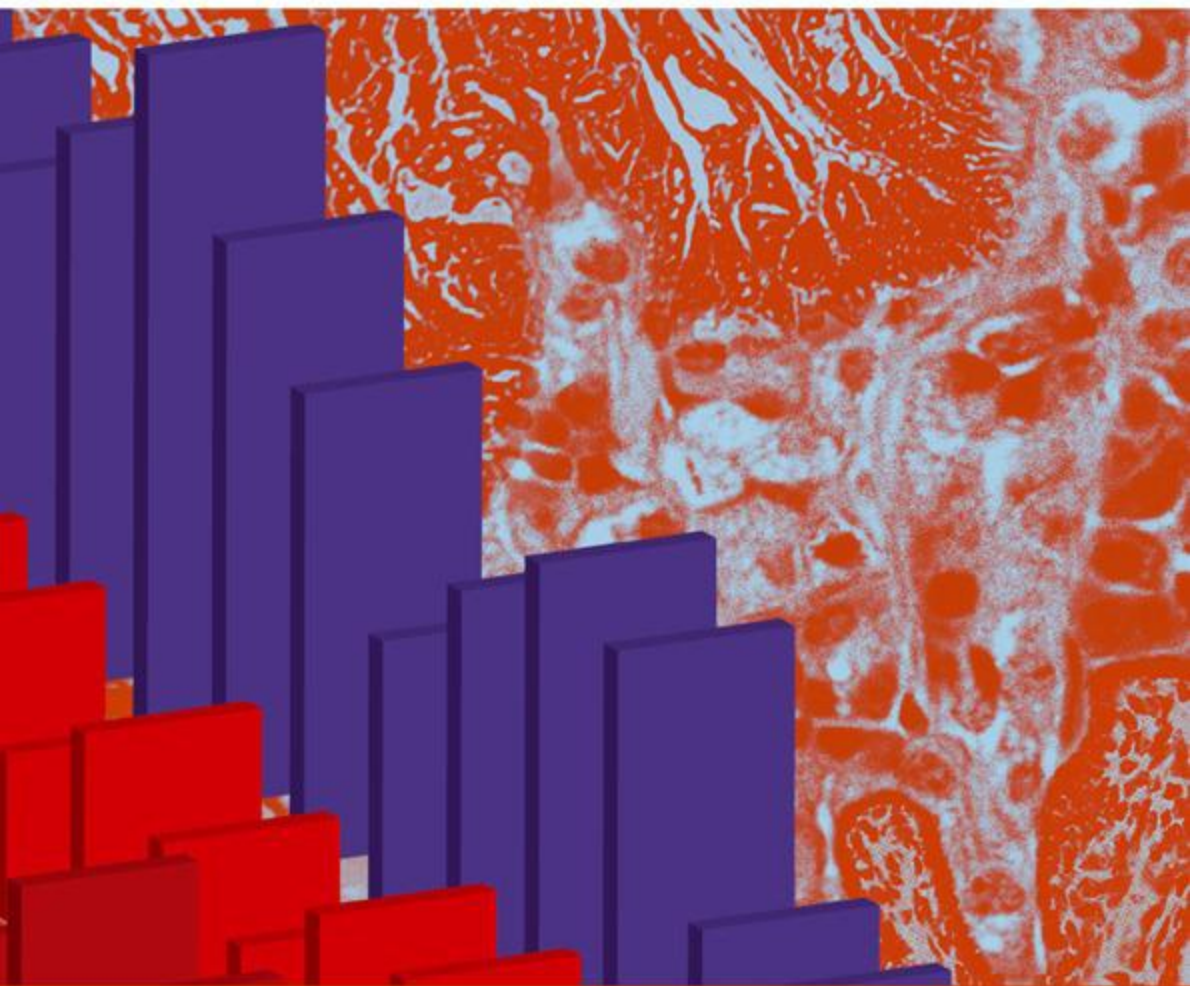
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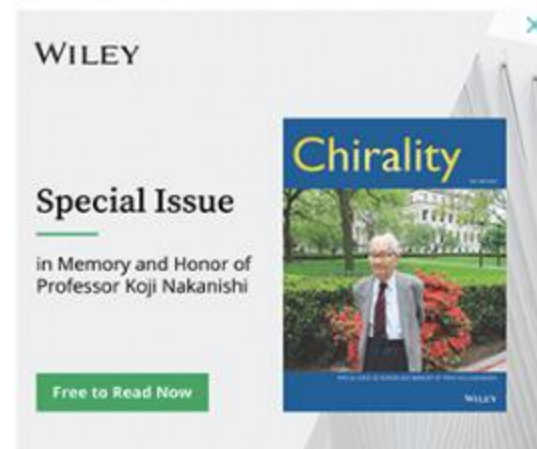
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Journal of Applied Toxicology publishes reviews and research articles on mechanistic, fundamental and applied research relating to the toxicity of drugs and chemicals at the molecular, cellular, tissue, target organ and whole body level *in vivo* (by all routes of exposure) and *in vitro/ex vivo*. Focus is on toxicogenomics and proteomics, teratogenesis/developmental/reproductive toxicology, carcinogenesis, mutagenesis, pharmacokinetics, pharmacotoxicological and metabolic mechanisms, risk assessment, environmental toxicology and environmental health as applied to humans (including epidemiological studies).

In addition *Journal of Applied Toxicology* also publishes analytical and method development studies, mechanistic and molecular toxicology studies on novel or existing drugs and chemicals, addressing important or topical aspects of toxicology. Special emphasis is given to papers of clear relevance to human health and regulatory pharmaceutical/chemical toxicology.

Authors wishing to submit a manuscript on chemical weapons material's should contact the Editor-in-Chief first (see instructions for authors).

Volume 37 Number 5, May 2017

Review article

In this table, we have shown that DON induced liver damage with positive and negative results in different animal models and cell lines. This mycotoxin can evoke obvious pathological changes in tissue by altering expressions of relative enzymes or oxidative stress. Otherwise, DON can induce expressions of apoptotic proteins thereby producing hepatic fibrosis and other kinds of liver damage.

Current sights for mechanisms of deoxynivalenol-induced hepatotoxicity and prospective views for future scientific research: A mini review 518

Z. Peng, L. Chen, A. K. Nüssler, L. Liu and W. Yang

Research articles

Here is presented a comprehensive investigation of the distribution of polyvinylpyrrolidone (PVP)-stabilized AgNP (20 or 110 nm) in pregnant rats after a single injection or oral gavage dose. The biological impacts of AgNP exposure were evaluated by metabolomic analysis, and measurement of biomarkers of cardiovascular injury, oxidative stress and inflammation. The investigation provided a basic understanding of the distribution, internal dose, persistence, metabolomics and elimination of AgNP after exposure in pregnant rats.

Disposition of intravenously or orally administered silver nanoparticles in pregnant rats and the effect on the biochemical profile in urine 530

T. R. Fennell, N. P. Mortensen, S. R. Black, R. W. Snyder, K. E. Levine, E. Poitras, J. M. Harrington, C. J. Wingard, N. A. Holland, W. Pathmasiri and S. C. J. Sumner

The acyl glucuronide (AG) metabolites of carboxylic acid-containing drugs are suggested to be implicated in toxicity, including hepatotoxicity. However, whether AG formation is related to toxicity *in vivo* remains unknown. We found that pretreatment of mice with the UDP-glucuronosyltransferase inhibitor (-)-borneol alleviated diclofenac (DIC)-induced acute liver injury by suppressing neutrophil infiltration into the liver. Thus, DIC-AG is partly involved in the pathogenesis of DIC-induced acute liver injury in mice by activating innate immunity.

Toxicological role of an acyl glucuronide metabolite in diclofenac-induced acute liver injury in mice 545

S. Oda, Y. Shirai, S. Akai, A. Nakajima, K. Tsuneyama and T. Yokoi

Contents continued

In this study, the effect of PFOA on the degranulation of mast cells and mast cell-mediated allergic inflammation in the presence of FcεRI cross-linking was evaluated. In immunoglobulin (Ig) E-stimulated mast cells, PFOA increased the release of histamine and β-hexosaminidase by the up-regulation of intracellular calcium levels. PFOA enhanced gene expression of several pro-inflammatory cytokines, including tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and IL-8 by the activation of nuclear factor (NF)-κB in IgE-stimulated mast cells.

Association between perfluorooctanoic acid exposure and degranulation of mast cells in allergic inflammation 554

J.-K. Lee, S. Lee, M.-C. Baek, B.-H. Lee, H.-S. Lee, T. K. Kwon, P.-H. Park, T.-Y. Shin, D. Khang and S.-H. Kim

Because different metals are used in complementary medicine for the treatment of diseases related to a dysfunction of the immune system, this study aimed at determining the immunomodulatory potential of Pb(NO₃)₂, AuCl₃, Cu(NO₃)₂, HgCl₂, AgNO₃, SnCl₂, AsCl₃ and SbCl₃ and possible toxic side effects of metal preparations. The results show that only copper preparations are promising to have immunomodulatory effects. Comparative analyses with upper limits of metals in the drinking water further showed that toxic side effects of low-concentrated metal preparations are improbable.

Immunomodulatory effects of metal salts at sub-toxic concentrations 563

C. Steinborn, C. Diegel, M. Garcia-Käufer, C. Gründemann and R. Huber

Until now, the role of arsenic (As₂O₃) in oxidative stress-mediated PARylation and DNA damage is elusive. We observed that oxidative stress (H₂O₂)-induced PARylation was suppressed by As₂O₃ exposure in cancer cells. As₂O₃ treatment promoted H₂O₂-induced DNA damage and apoptosis, leading to increased cell death. We found that *N*-ethylmaleimide can reverse As₂O₃-mediated effects, thus enhancing PARylation and reducing DNA damage with attenuated cell death in a glutathione-dependent manner. Our findings identify *N*-ethylmaleimide as a potential antidote against As₂O₃-mediated DNA damage.

Antagonistic effect of *N*-ethylmaleimide on arsenic-mediated oxidative stress-induced poly(ADP-ribosyl)ation and cytotoxicity 573

A. S.-S. Wang, Y.-T. Chou and Y.-S. Pu

Bjerkandera adusta (*B.ad*) and benzo[*a*]pyrene (BaP) each activated antigen-presenting cells (APCs) in the presence and the absence of heated Asian sand dust particles (H-ASDs). H-ASDs alone slightly activated APCs. The activation induced by *B.ad* was more apparent than that by BaP in the presence and absence of H-ASDs. *B.ad* rather than BaP contributes to the exacerbation of asthma regardless of the presence or absence of sand particles, particularly by activation of the immune system via APCs.

Biological factor related to Asian sand dust particles contributes to the exacerbation of asthma 583

A. Honda, T. Sawahara, T. Hayashi, K. Tsuji, W. Fukushima, M. Oishi, G. Kitamura, H. Kudo, S. Ito, S. Yoshida, T. Ichinose, K. Ueda and H. Takano

Effects of acidic, basic and neutral fractions of water soluble organic compounds from oil sands process water (OSPW) on the function of P-glycoprotein (P-gp) were investigated using Caco-2 cells and larvae of Japanese medaka. Basic and neutral fractions inhibited P-gp. Acute toxicity, accumulation, bioconcentration, and half-life of chlorpyrifos, a model compound used as a substrate of P-gp, were greater in larvae co-exposed with a mixture basic and neutral compounds. Results support chemosensitization as a potential mechanism of toxicity of OSPW.

Toxicokinetics and toxicodynamics of chlorpyrifos is altered in embryos of Japanese medaka exposed to oil sands process-affected water: evidence for inhibition of P-glycoprotein 591

H. A. Alharbi, J. Alcorn, A. Al-Mousa, J. P. Giesy and S. B. Wiseman

Contents continued

In the present study, we described the developmental toxicity of auranofin. The biochemical levels of oxidative stress enzymes as well as the expressions of a series of genes related to oxidative stress, cardiac, metal stress and pigment formation were detected. Our findings may help gain a better insight into the molecular mechanisms underlying AF-induced development defects.

Developmental toxicity of auranofin in zebrafish embryos 602

X.-Y. Gao, K. Li, L.-L. Jiang, M.-F. He, C.-H. Pu, D. Kang and J. Xie

IL-6 and IL-8 mRNA expression was maximally induced by 10 μ M methylmercury (MeHg) in U937 macrophages at 6 h and declined after 24 h of exposure. Involvement of RelA and p50 in MeHg-induced IL-6 and IL-8 activation was shown by siRNA knock down experiments. Exposure to 4 μ M MeHg also induced mRNA and protein of IL-8 expression in U-87 MG cells. Five mM *N*-acetyl-L-cysteine suppressed MeHg-induced activation of IL-6 and IL-8 mRNA expression in U937 macrophages.

Activation of interleukin-6 and -8 expressions by methylmercury in human U937 macrophages involves RelA and p50 611

M. Yamamoto, N. Khan, M. Muniroh, E. Motomura, R. Yanagisawa, T. Matsuyama and C. F. A. Vogel

Inhalation, but not drinking-water exposure, to a high concentration of ethyl tertiary butyl ether was reported to cause liver tumors in male rats. Using a PBPK model for ethyl tertiary butyl ether and its metabolite tertiary butyl alcohol, under cancer bioassay exposure scenarios, showed a shift from linear to nonlinear kinetics at the exposure concentration associated with liver tumors. This suggests that a liver tumor mode of action that occurs under a high exposure concentration is not relevant for assessing human risk.

Physiologically based pharmacokinetic model for ethyl tertiary-butyl ether and tertiary-butyl alcohol in rats: Contribution of binding to α 2u-globulin in male rats and high-exposure nonlinear kinetics to toxicity and cancer outcomes 621

S. J. Borghoff, C. Ring, M. I. Banton and T. L. Leavens

Developmental toxicity of auranofin in zebrafish embryos

Xiao-Yan Gao, Kang Li, Ling-Ling Jiang, Ming-Fang He, Cun-Hai Pu, Dongzhou Kang , Jingjing Xie First published: 04 November 2016 | <https://doi.org/10.1002/jat.3410> | Citations: 13[Read the full text >](#)

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Abstract

Auranofin (AF) is used in clinic for the treatment of rheumatoid arthritis, repurposing of AF as an anticancer drug has just finished a phase I/II clinical trial, but the developmental toxicity of AF remains obscure. This study focused on its developmental toxicity by using zebrafish embryos. Zebrafish embryos were exposed to different concentrations (1, 2.5, 5, 10 μM) of AF from 2 h post-fertilization (hpf) to 72 hpf. At 72 hpf, two major developmental defects caused by AF were found, namely severe pericardial edema and hypopigmentation, when embryos were exposed to concentrations higher than 2.5 μM . Biochemical detection of oxidative stress enzyme combined with expressions of a series of genes related to oxidative stress, cardiac, metal stress and pigment formation were subsequently tested. The superoxide dismutase activity was decreased while malondialdehyde content was accumulated by AF treatment. The expression of oxidative stress-related genes (*sod1*, *gpx1a*, *gst*), pigment-related genes (*mitfb*, *trp-1a*) and one metal stress-related gene *ctr1* were all decreased by AF exposure. The expressions of cardiac-related genes (*amhc*, *vmhc*) and one metal-related gene *hsp70* were found to be significantly upregulated by AF exposure. These findings indicated the potential developmental toxicity of AF on zebrafish early development. Copyright © 2016 John Wiley & Sons, Ltd.

Physiologically based pharmacokinetic model for ethyl tertiary-butyl ether and tertiary-butyl alcohol in rats: Contribution of binding to $\alpha 2u$ -globulin in male rats and high-exposure nonlinear kinetics to toxicity and cancer outcomes

Susan J. Borghoff^{a,b}, Caroline Ring^b, Marcy I. Banton^b and Teresa L. Leavens^c

ABSTRACT. In cancer bioassays, inhalation, but not drinking water exposure to ethyl tertiary-butyl ether (ETBE), caused liver tumors in male rats, while tertiary-butyl alcohol (TBA), an ETBE metabolite, caused kidney tumors in male rats following exposure via drinking water. To understand the contribution of ETBE and TBA kinetics under varying exposure scenarios to these tumor responses, a physiologically based pharmacokinetic model was developed based on a previously published model for methyl tertiary-butyl ether, a structurally similar chemical, and verified against the literature and study report data. The model included ETBE and TBA binding to the male rat-specific protein $\alpha 2u$ -globulin, which plays a role in the ETBE and TBA kidney response observed in male rats. Metabolism of ETBE and TBA was described as a single, saturable pathway in the liver. The model predicted similar kidney AUC_{0-24} for TBA for various exposure scenarios from ETBE and TBA cancer bioassays, supporting a male rat-specific mode of action for TBA-induced kidney tumors. The model also predicted nonlinear kinetics at ETBE inhalation exposure concentrations above ~2000 ppm, based on blood AUC_{0-24} for ETBE and TBA. The shift from linear to nonlinear kinetics at exposure concentrations below the concentration associated with liver tumors in rats (5000 ppm) suggests the mode of action for liver tumors operates under nonlinear kinetics following chronic exposure and is not relevant for assessing human risk. Copyright © 2016 The Authors. Journal of Applied Toxicology Published by John Wiley & Sons Ltd

Additional supporting information may be found in the online version of this article at the publisher's website.

Keywords: ethyl tertiary-butyl ether; PBPK model; tertiary-butyl alcohol; $\alpha 2u$ -globulin; nephrotoxicity

Introduction

Ethyl tertiary-butyl ether (ETBE, CAS RN 637-62-3) is used as a fuel oxygenate in unleaded gasoline to improve combustion efficiency, allowing the gasoline to burn more completely and thereby reducing exhaust emissions. The technical characteristics of ETBE suggest that it is comparable to methyl tertiary-butyl ether (MTBE), a fuel oxygenate that had been more widely used until it was found to be mobile in groundwater. Based on concerns for contamination of drinking-water sources (Malvest et al., 2005), MTBE was removed from the US market. However, the much lower water solubility of ETBE (25.7 g/l), compared to MTBE (42 g/l), is considered an advantage, because its mobility in groundwater will be lower than that of MTBE in the event of leakage from an underground storage tank (McGeehan, 2007).

In the past 15 years, ETBE has not been used significantly as a gasoline additive in the USA and Europe. The US Geological Survey (2008) USGS Circular, 1262 reported that ETBE was detected in less than 0.5% of public wells at concentrations of $<0.2 \mu\text{g l}^{-1}$, with less frequent detection in domestic wells. In Japan, ETBE-blended gasoline has been used since 2007 (Ehali et al., 2011). The maximum atmospheric concentration of ETBE in the general environment is estimated to be $\sim 0.007 \text{ ppm}$ (JPC, 2006a). Ehali et al. (2011)

reported that in Japan the geometric mean of 8-h time-weighted average exposure (TWA-8h) to ETBE was 0.08 ppm (0.02–0.28 ppm) for 28 gas-station workers and 0.04 ppm (0.01–0.27 ppm) in two gasoline tanker truck drivers. None of the essential workers had a TWA-8h exceeding the American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV) of 5 ppm, which was the threshold recommended by the ACGIH at the time the Etali et al. (2011) study was published. The current occupational ACGIH TLV established for ETBE is zero.

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