Diphenylarsinic acid (DPAA) was detected as the major compound in the arsenic poisoning incident in Kamisu, Ibaraki, Japan, in 2003. DPAA is a non-natural pentavalent organic arsenic, and people who had used this arsenic-contaminated well water developed cerebellar symptoms such as tremor, lightheaded, and ataxia. It is important to elucidate the molecular mechanism of toxicity of DPAA for the prevention and treatment against the DPAA incident, because the precise mechanism of these symptoms induced by DPAA has not been clear yet. Previously, we have elucidated that DPAA affected specifically astrocytes rather than neurons in vitro and in vivo rat cerebellum. In selectively cultured normal rat cerebellar astrocytes (NRA), DPAA at 10 μM for 96 h increased the phosphorylation of MAP kinases (ERK1/2, p38MAPK, and SAPK/JNK), the expression and/or the phosphorylation of transcription factors (CREB, c-Jun, and c-Fos), the expression of oxidative stress-responsive factors (HO-1, Nrf2, and Hsp70), and the secretion of glutathione into culture medium. In the present study, concerning human exposure risk, we tried to evaluate, in cultured normal human cerebellar astrocytes (NHA) the DPAA-induced aberrant activation confirmed in NRA and compared the degree of DPAA-induced aberrant activation in NHA and NRA. While NRA were exposed to 10 μM DPAA in serum-free medium (DMEM/F-12 supplemented with insulin, transferrin, and selenite (DMEM/F-12/ITS) for 96 h, NHA were exposed to 10, 20, or 50 μM DPAA in DMEM/F-12/ITS for 96 h or 10 μM DPAA for 96, 144, 192, 240, or 288 h, and their protein expression levels and concentrations of glutathione were analyzed using western blotting and Glutathione (GSSG/GSH), detection kit, respectively. Although, in NRA, 10 μM DPAA for 96 h induced significant aberrant activation, exposure to 10 μM DPAA for 96 h had little effect in NHA. In contrast, 50 μM DPAA for 96 h or 10 μM DPAA for 288 h could induce significant aberrant activation of NHA as observed in NRA exposed to 10 μM for 96 h. These results suggested that NHA was more resistant than NRA against exposure to DPAA in a dose-and time-dependent manner. In addition, the long latency in DPAA toxicity suggested that DPAA could affect NHA as well as NRA indirectly, where DPAA might be metabolized intracellularly into more active compounds by particular processes such as glutathione conjugation.