



High-dose acute exposure of paraquat induces injuries of swim bladder, gastrointestinal tract and liver via neutrophil-mediated ROS in zebrafish and their relevance for human health risk assessment

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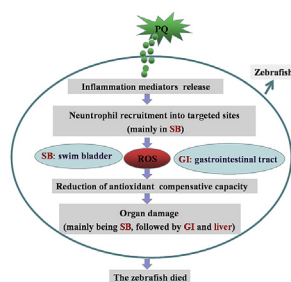
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HIGHLIGHTS

- The primary target organs of PQ were swim bladder, followed by gastrointestinal tract and liver.
- PQ enhanced leukocyte recruitment into swim bladder and induced ROS which can be scavenged by glutathione.
- qRT-PCR results showed that PQ increased the expression level of genes involved in the inflammatory response.
- Acute exposure of PQ induced target organ toxicity maybe via neutrophil-mediated ROS in zebrafish.

GRAPHICAL ABSTRACT



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ABSTRACT

The exact toxicological mechanisms of paraquat (PQ) poisoning are not entirely clear, especially on the high-level acute exposure. To assess the health risk of PQ, especially to suicidal individuals, accidental ingestion eaters, occupational groups, and special multitude, firstly we explored the acute toxic effect and the possible mechanisms of high-level exposure of PQ using zebrafish. The mainly target organs of PQ were swim bladder which is the homolog of the mammalian lung, followed by gastrointestinal tract and liver. Morphological malformations which were further defined by histopathologic examination include smaller size, fibrosis and inflammatory cell invasion for swim bladder; irregularly arranged or dissolved epithelial folds, loss of villous architecture, and ecclasis of mucosal cells in a smaller lumen for gastrointestinal tract; as well as smaller size, degeneration, fibrous proliferation, atrophy for liver. In addition, PQ enhanced leukocyte recruitment (neutrophil migrated first, followed by macrophage) into swim bladder and induced ROS which can be scavenged by glutathione. Moreover, qRT-PCR results showed that PQ increased the expression level of genes involved in the inflammatory response, such as *L-1β*, *IL-6*, *IL-8*, *TNF-α*, *TNF-β*, *IFN-1*, *TGF-β*, and *NF-kB*. For the first time, our results demonstrated that acute exposure of PQ induced pulmonary toxicity which was followed by gastrointestinal and hepatic toxicity via neutrophil-mediated ROS in zebrafish. In summary, these findings generated here will contribute to our better understanding of characteristics of PQ acute poisoning and can provide valuable information

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on better PQ poisoning treatments, occupational disease prevention, and providing theoretical foundation for risk management measures.

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1. Introduction

Paraquat (PQ; 1,1'-dimethyl-4,4'-bipyridinium) is a non-selective and broad-spectrum herbicide that has been widely used in agriculture in many countries since the 1960s (Sun et al., 2016; Li et al., 2014), because it is fast acting and non-persistent in the environment (Ko et al., 2017). However, ingestion of the concentrated formulation is very toxic to humans with mortality rate at approximately 50%–90% (Xie et al., 2016). This high mortality is primarily attributed to the lack of understanding of PQ-induced toxicity to humans. Furthermore, there are still no specific antidote or conclusively effective therapies to treat paraquat poisoning (Gil et al., 2014). The sale of paraquat has been banned in Europe since 2007 (Ko et al., 2017) and many other countries, such as South Korean (banned from 2012; Cha et al., 2014) and results will be apparent thereafter. Ko and his coworkers reported that the number of associated poisonings indeed decreased after the paraquat ban (Ko et al., 2017). However, in China, although the traditionally used PQ solution has been banned on use and sale since 2016 (The news website, 2012), a granule and emulsion preparation instead is still used in large (Lin et al., 2017), suggesting that the risk of PQ exposure and poisoning still exist, especially to suicidal individuals, accidental ingestion eaters, occupational groups, and special multitude including pregnant women, babies, young children, sick people, the elderly, or anyone whose health is compromised.

The exact toxicological mechanisms of PQ poisoning are not entirely clear (Lin et al., 2017), although it has been widely studied all the time using cell lines, invertebrate model species (e.g., *Drosophila* and *C. elegans*) and mammals including rat, mouse, dog, sheep, swine (Huang et al., 2016; Shukla et al., 2016; Gourgou and Chronisa, 2016; Kanwar, 2015; Wang et al., 2016). Cell-based assays which limits the screens to cell-autonomous phenotypes or those end points that can be observed in relatively simple culture systems provide limited information about the absorption, distribution, metabolism, excretion and toxicity of the compounds (Macrae and Peterson, 2015). *In vitro* models are artefactual in that they cannot fully reproduce the conditions of *in vivo* exposure (Boraschi and Italiani, 2016); so they are limited by the availability of fully phenotypically and physiologically characterised cell systems. For *in vivo* invertebrate models, such as *C. elegans* and *Drosophila*, the anatomical and physiological simplicity make them may not simulated the actual conditions associated with the human poisoning process, which may hinder research efforts to understand disease mechanisms (Cunliffe et al., 2015). For mammalian systems (i.e. rat and rabbit), they showed low predictive values to man, when potential hazard for development and reproduction is considered (Sun et al., 2016); So the testing results based on mammalian studies may deviate from the actual profile of toxicity in some cases, especially for screening of toxic target organs; Moreover, mammalian experimentation are requirement of skilled/trained manpower (Doke and Dhawale, 2015). So for example, *in vivo* observations need 3D imaging systems which has not been widely used (Wang et al., 2016). Furthermore, with the increasing implementation of 3R principles (reduce, refine and replace) in many European countries, USA, Japan, and other developed and developing countries, the number of mammals used in

experiments is smaller and smaller. Besides increasingly concern of ethics, very high cost involved in breeding, housing and lengthy protocols of animal experiments is another drawback (Doke and Dhawale, 2015). Therefore, there is an urgent need to develop an animal model for new toxicity testing assays that are robust and can be performed with low cost and high throughput based on non-invasive whole- and live-organisms, especially for screening of toxic target organs.

Here we describe a novel *in vivo* model: zebrafish (*Danio rerio*). The excellent biological characteristics (e.g. small size, easy breeding and high fecundity; short life cycle, rapid development of embryo, transparent embryo and body; Lucas et al., 2014; Wang et al., 2016) and high conservation of gene function and many molecular pathways compared with their human orthologues (Liu et al., 2017b), have made zebrafish emerge as a prominent vertebrate model system based on phenotype for disease modelling (Schartl, 2014; Gurevich et al., 2015), drug screening (Baraban et al., 2013; Veinotte et al., 2014), pharmacology (Levin et al., 2015; Wijk et al., 2017), target identification (Schenone et al., 2013; Shen et al., 2015), and toxicology (Asharani et al., 2011; McGee et al., 2013; Dai et al., 2014; Chakraborty et al., 2016). Zebrafish larvae possess the most homologs of human including heart, intestine, liver, kidney, skin, skeletal muscles, spleen, central nervous system, siwm bladder (SB; be homologous to lung; Zhang et al., 2016), and so on. In an intact zebrafish (*in vivo*) assays, compounds tested can exhibit the ability to be absorbed, reach the target tissue, and avoid rapid metabolism and excretion (Macrae and Peterson, 2015). As such, the tested compounds can exert a diverse profile of biological processes and cover a much broader range of toxic effects based on phenotypes. Such features are especially helpful to the screening and identification of toxic target organs in toxicity testing assays. Moreover, this transparent vertebrate can support some research that cannot be performed in other model systems (Liu et al., 2017b). For example, α and β splice variants of glucocorticoid receptor in zebrafish are remarkably similar to humans, but are not found in other mammals such as mice and rats. (Alsop and Vijayan, 2009). Furthermore, zebrafish until 5 days post fertilization (5dpf) are not considered animals in accordance with relevant animal welfare acts and regulations (Racza et al., 2017). So the zebrafish has proven to a very good *in vivo* model system (Badyal and Desai, 2014). Therefore, in order to investigate the target organs in the acute toxicity of PQ poisoning and further explore its underlying possible mechanisms, zebrafish model was employed in the present study. To our knowledge, this is the first study, according to the health risk assessment, to systematically and thoroughly examine the PQ-induced toxicity and its potential mechanism using the whole zebrafish as an *in vivo* model.

2. Materials and methods

2.1. Zebrafish handling

Adult zebrafish (*Danio rerio*) including wild-type AB strain and transgenic strain [Tg (mpo:GFP) and Tg (zlyz:EGFP)] were maintained and fed as our described previously (Liu et al., 2017a). Two females and one male adult zebrafish with age 16 months after fertilization were transferred to a spawning box containing water

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