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**Urinary excretion of 3-phenoxybenzoic acid in  
middle-aged and elderly general population of Japan**

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## **Abstract**

Limited data are available on the background levels of exposure to synthetic pyrethroid (PYR) in Japan despite their frequent application for agriculture and indoor extermination and possible effects of chronic and/or low-dose PYR exposure on human health. This study was conducted to describe the level and distribution of one of the major PYR metabolites, 3-phenoxybenzoic acid (3-PBA), in urine samples collected from a general population in Japan. The subjects were 535 individuals (184 men and 351 women;  $61.5 \pm 9.8$  years of age, mean  $\pm$  S.D.) residing in a town in Hokkaido, a dairy and agricultural area. Urinary 3-PBA was found detectable in 98% of samples above the limit of detection of 0.02  $\mu\text{g/L}$ . The geometric mean values of urinary 3-PBA in occupationally exposed farmers ( $n = 87$ ) and the remaining general group without occupational exposure ( $n = 448$ ) were 0.38  $\mu\text{g/L}$  and 0.29  $\mu\text{g/L}$ , respectively, ranging from  $< \text{LOD}$  to 17.09  $\mu\text{g/L}$ . No significant differences in urinary 3-PBA concentrations were shown between these two groups. Moreover, 3-PBA concentrations were found comparable to those reported in some countries. The present study is, to our knowledge, the first report of a biological monitoring study of urinary 3-PBA, which elucidated the background environmental exposure level of PYR in the Japanese general population without occupational exposure. Further nationwide studies covering different seasons and age distribution are needed to monitor the urinary 3-PBA levels in Japan.

*Keywords:* pyrethroids, 3-phenoxybenzoic acid, general population, Japanese, exposure assessment

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**Ethics approval:**

This study protocol was reviewed and approved by the Ethical Committee of Nagoya University Graduate School of Medicine, and all subjects provided their written informed consent.

## 1. Introduction

The widespread use of pesticides in agricultural settings, public health, commerce, and individual households throughout the world is an indication of the importance of these compounds. According to the official statistics in Japan, annual domestic production and import of such pesticides as organophosphorus (OPs), synthetic pyrethroids (PYRs), and neonicotinoid amounted to 25,000 and 5,000 tons of active components, respectively (Nouyaku-Youran, 2006). An OECD report revealed that Japan's consumption of pesticides as active component estimated at 1.50 ton/km<sup>2</sup> arable and permanent cropland in 1990s is much higher than those of other developed countries (US; 0.21 ton/km<sup>2</sup>, Germany; 0.29 ton/km<sup>2</sup>, Italy; 0.78 ton/km<sup>2</sup>) (OECD Environmental Performance Reviews JAPAN). Given these estimates about the national-level pesticide consumption, the general population in Japan is assumed to be exposed to pesticides in higher doses from a variety sources than in other countries.

Among the classes of widely recognized pesticides, PYRs have today become the most frequently used one for non-occupational as well as occupational purposes. In the United States, regulatory phaseout of OPs for residential pest control caused the use of PYR to increase since the late 1990s (Current Occupational & Environmental Medicine. 4th edition); replacement of OPs with PYRs in residential environments has also been observed in Japan. Thus far, research on PYR toxicity has primarily focused on the acute, short-term effect, i.e. prolonged depolarization and hyperexcitation of the nervous system caused by its interaction with sodium channels of the axon (Narahashi et al., 1982; Tabarean and Narahashi, 2001). However, the effect of long-term exposure to low-level PYRs on human health has been little characterized. A number of epidemiological studies have suggested the relationship between Parkinson's disease (PD) and environmental exposure to pesticides (Tanner and Langston, 1990; Gorell et

al., 1998; Priyadarshi et al., 2001); a recent experimental study corroborated the possible underlying mechanism that in vivo exposure to PYRs, deltamethrin and permethrin, increases dopamine transporter and transporter-mediated dopamine uptake in the striatal synaptosome (Elwan et al., 2006). Also revealed by a recent study was the estrogenicity of PYR metabolites (McCarthy et al., 2006). As a consequence of these etiological findings, there has been a growing concern over the association between the long-term exposure to PYRs and as-yet-unknown adverse health effects in human.

In the human body, PYRs are metabolized by carboxylesterase, and via further metabolization renally excreted in various forms; among them, 3-phenoxybenzoic acid (3-PBA) is a non-specific, most frequently detected metabolite of major PYRs including permethrin, cypermethrin, deltamethrin, sumithrin, etofenprox and cyhalothrin. Until now, the analytical technique of 3-PBA has become so sophisticated that it can be used as a biomarker to assess the level of occupational as well as environmental PYR exposure which occurs even in daily activities of life through various routes (ingestion, inhalation and dermal absorption).

In our previous study, 3-PBA has been quantified in the urine of pest control operators (PCOs) exposed to PYR during handling, mixing, and spraying (Wang et al., 2007). In the absence of data on the urinary 3-PBA levels derived from non-occupational PYR exposure, however, we considered that risks resulting from PYR exposures among PCOs might not be adequately assessed. Although some studies abroad detected 3-PBA in urine samples of the general population (Becker et al., 2006; Schettgen et al., 2002; Heudorf, 2001; Saieva, 2004), to our knowledge no such study has been conducted in Japan. The primary objective of this study is to describe the distribution of urinary 3-PBA levels in spot urine samples among different healthy

populations in Japan according to gender and age groups. We then further summarized our data to compare with the results available from similar studies conducted on general populations in other countries.

## **2. Materials and methods**

### *2.1. Study subjects and sample collection*

The study subjects were 184 men and 351 women aged 39-85 recruited from 535 residents in a rural area of Hokkaido, Japan, who attended a health checkup program in August 2005. Our self-administered questionnaire revealed that 88 subjects have been engaged in farm work involving the spraying of pesticides; the mean age  $\pm$  S.D. of farmers and non-farmers was  $61.9 \pm 9.7$  and  $61.4 \pm 9.9$ , respectively. They underwent an annual health checkup which included a self-administered questionnaire, a physical examination and collection of fasting blood and spot urine samples. Prior to enrollment in the study, an informed consent form was signed by each subject giving the right to the use of personal information for research purposes. The questionnaire addressed such lifestyle characteristics as physical activity, smoking status, drinking habits, and occupation. The Ethics Committee of the Nagoya University Graduate School of Medicine, Nagoya, Japan approved the study protocol.

Collected spot urine samples were immediately measured for screening urinalysis while the rest were aliquoted into 10 ml polyethylene tubes and shipped daily at  $-20^{\circ}\text{C}$  to our laboratory, and then stored at  $-80^{\circ}\text{C}$  until 3-PBA assay.

### *2.2. Materials*

2-PBA as internal standard (I.S.) and 3-PBA were purchased from Tokyo Kasei Kogyo (Tokyo, Japan). 1, 1, 1, 3, 3, 3-Hexafluoroisopropanol (HFIP),

*N,N*-diisopropylcarbodiimide (DIC), *tert*-butyl-methyl-ether (*t*-BME), sodium hydrogen carbonate and iso-octane were from Sigma-Aldrich (St. Louis, MO, USA). All other reagents were of analytical grade purity.

### 2.3. 3-PBA analysis

The concentration of 3-PBA in urine were measured by gas chromatography-mass spectrometry (GC/MS) equipped with an electro-ionization system according to a method established previously (Leng et al., 2005). Briefly, 2 ml urine samples were transferred in a 15-ml screw-top glass test tube, and 20  $\mu$ l of I.S. solution (8 mg 2-PBA/ml of acetonitrile) and 0.5 ml of 6 mol/L HCl were added. After gentle shaking, the test tube was incubated at 100 °C in a heat block for hydrolyzation. After cooling the test tubes on ice, 4 ml of *tert*-butyl-methyl-ether was added, and the mixture was shaken vigorously for 10 min and centrifuged for 5 min at 2,000  $\times$  g. The organic phase (upper layer) was transferred in a new screw cap test tube. The residuals were re-extracted with 4 ml of *tert*-butyl-methyl-ether, shaken and centrifuged. The supernatant obtained from second extraction was combined with the first extract. The resulting extract was evaporated at 45 °C (heat block) to dryness with a gentle nitrogen stream. The residue was dissolved in 250  $\mu$ l acetonitrile. For derivatization, 30  $\mu$ l of HFIP and 20  $\mu$ l DIC was added and incubated for 10 min at room temperature. Then, 1 ml of a 1 mol/l sodium hydrogencarbonate solution and 250  $\mu$ l iso-octane was added. The test tube was shaken vigorously and centrifuged for 5 min at 2,000  $\times$  g. One  $\mu$ L of the *iso*-octane phase was injected into GC/MS.

Analyses of 3-PBA were performed on Agilent 5975 inert MSD system. The GC operating conditions were as follows: GC column, HP-5MS (Agilent, USA), 30 m  $\times$  0.25-mm i.d., 0.25- $\mu$ m film thickness; column temperatures, 70 °C (1 min)-15 °C



/min-300 °C (6 min); injection port temperature, 250 °C; carrier gas, helium (99.999% purity); flow rate, 1 ml/min. The injection volume was 1 µl. Splitless was changed to split 15:1 at 2 min after sample injection. The MS operating conditions were as follows: ionization source temperature, 230 °C; electron ionization, 70 eV; interface temperature, 300 °C. All urinary creatinine levels were measured according to the Jaffé reaction.

#### 2.4. *Quality control materials*

Two “Quality Control” urine samples were used in the urinary 3-PBA assay. The urine samples from 3 healthy volunteers (students of Nagoya University, 22-29 years) were collected and pooled for “quality control” urine, then, standard 3-PBA solution dissolved in acetonitrile was added. Consequently, the final concentration of 3-PBA in quality control urine was estimated to be 2.3 and 46.9 µg/L using above mentioned measurement technique. These quality control urine samples were stored at -80 °C until analysis, and analyzed every 18 samples. The method of urinary 3-PBA analysis used in this study showed good reproducibility on a 10-replicate measurement of pooled control urine (intra-assay coefficient of variation of 5% with 2.3 µg/L and 8% with 46.9 µg/L), sensitivity (LOD = 0.02 µg/L, signal to noise ratio = 1:10), and relative recovery (98%), and thus was considered to be suitable for routine analysis.

#### 2.5. *Statistical analysis*

Deviation from the normality of the data distribution was examined using a Kolmogorov- Smirnov test. Mann-Whitney *U* test and Kruskal-Wallis test were used to examine the differences in urinary 3-PBA concentrations between men and women and between 3 age groups (40-49, 50-69, 70-85), respectively. All statistical analysis

was conducted using the SPSS statistical package for Windows version 11.0J (SPSS Inc., Chicago, IL), and 2-sided  $p$  values of  $< 0.05$  were considered statistically significant. Undetectable urinary 3-PBA concentrations were estimated as half the limit of detection (LOD) value (Finkelstein et al., 2001).

### 3. Results

Detection rates ( $> \text{LOD}$ ) were 98% for non-farming group and 99% for farming group. The urinary creatinine concentration in men ( $1.24 \pm 0.69 \text{ g/L}$ ) was significantly higher than in women ( $0.80 \pm 0.58 \text{ g/L}$ ). Both the distribution of uncorrected 3-PBA ( $\mu\text{g/L}$ ) and creatinine-corrected 3-PBA ( $3\text{-PBA}_{\text{cre}}$ ) concentrations ( $\mu\text{g/g}$  of creatinine) in the non-farming group are presented in Table 1. The Kolmogorov-Smirnov test indicated that the distribution of  $3\text{-PBA}_{\text{cre}}$  was logarithmically normal. Urinary 3-PBA concentrations were not significantly different between 3 age groups, but the  $3\text{-PBA}_{\text{cre}}$  value in women was significantly higher than that in men. Table 2 presents the distribution of 3-PBA and  $3\text{-PBA}_{\text{cre}}$  values in the farming group. There were no significant differences in urinary 3-PBA concentrations between genders or age groups. Table 3 summarizes the results of previous studies, which reported urinary 3-PBA concentrations in general populations. The geometric mean (GM) of 3-PBA in non-farmers group in our population was close to that in Third National Report on Human Exposure to Environmental Chemicals (CDC 2005) and GerES IV Pilot study (Becker et al., 2006). Mean value of 3-PBA reported by Leng et al (2005) was  $0.37 \pm 0.77 \mu\text{g/L}$ , which is slightly lower than that in the non-farming group of our population ( $0.63 \pm 1.34 \mu\text{g/L}$ ). Mean value of 3-PBA reported by Saieva et al. (2004) was much higher than that in the non-farming group in our population.

#### 4. Discussion

This study merits attention in that it provided descriptive data concerning the distribution of urinary PYR metabolites in the healthy general population for the first time in Japan. The method for determining metabolites in the urine used in this study was the most practical and widely used one to estimate the internal doses of PYRs; this facilitated the comparison of the urinary 3-PBA concentrations obtained in our population with those reported abroad in regard to their distribution.

Obvious advantages of urine samples for biological monitoring of the metabolites are the ease of sample collection, dense concentration of the metabolite, and the greater number of samples available for analysis compared to blood samples. The detection of this metabolite in urine of the general population might reflect exposure to various PYRs via dietary intake and from residential environments. We supposed that, considering the non-specific nature of 3-PBA, the importance of its use as a monitoring marker is not to specify the sources and routes of the exposure which are usually diverse and hardly distinguishable, but to assess the overall PYR exposure levels covering all routes.

In our previous study, the GM of 3-PBA levels in urine collected from Japanese pest control operators in summer was 12.2  $\mu\text{g/g}$  creatinine (Wang et al., 2007), > 30-fold higher than GMs obtained in the present study. These results clearly indicated dramatically high levels of exposure among pest control operators in comparison with the non-spraying population. However, our study population showed no statistical difference in GM of 3-PBA between the farmers and non-farmers. Although no direct exposure assessment tool was incorporated in this study and hence the reason for this lack of difference remains unclear, we speculated that factors such as the pesticide application method or work practice peculiar to this area of the study might contribute;

the majority of the pesticide sprayers among our subjects were engaged in dairy farming, which involved much less frequent handling and spraying opportunities in summertime than pest control operators who usually work in indoor environments filled with mist or vapor of sprayed pesticides.

Barr et al (2007) performed a cross validation study between two methodological techniques for measurement of 3-PBA (Leng et al., 2005; Baker et al., 2004) and concluded that both methods produced comparable analytical results on urine samples at unknown concentrations. The most salient finding of our study is that the GM of 3-PBA levels of our subjects was virtually identical to those of a U.S. population (0.32  $\mu\text{g/L}$ ) and German population (0.34  $\mu\text{g/L}$ ). Saieva et al. (2004) reported much higher 24-hour urinary 3-PBA GMs of 0.88  $\mu\text{g/day}$  for 51 Italians who live in the urban area (Florence) and 0.71  $\mu\text{g/day}$  for 18 Italians who live in the rural area (Ragusa). Some precautions regarding the concentration unit of the metabolites ( $\mu\text{g/day}$  v.s.  $\mu\text{g/g}$  of creatinine) should be paid in the comparison of these results. Since the amount of creatinine excreted per day was assumed to vary around one gram, comparison of these data indicated that  $\approx$  3-fold variations of the urinary 3-PBA concentration even between low-level exposure populations are highly likely. In addition, the LOD levels differed greatly from study to study; although our study achieved a high detection rate, high level of LOD would result in low detection rate and cause the population distribution of the 3-PBA concentrations to heavily skew, undermining the appropriate characterization of PYR exposure in the general population.

We have estimated per cropland PYR shipment in 2005 at 1.72  $\text{kg/km}^2$  and 3.42  $\text{kg/km}^2$  in Hokkaido and all parts of Japan, respectively (cropland data were obtained from the Ministry of Agriculture, Forestry and Fisheries of Japan). These estimations implied that people who live in Hokkaido have generally been less exposed to

environmental PYR than average Japanese, though other information is lacking on exposures through drinking water, air, dust, and circulation of food products, both domestic and imported, in the market. We believe that the monitoring of urinary 3-PBA in other areas in Japan is to be conducted to help establish reliable reference data; moreover, seasonal variations of the monitoring data should also be cautiously considered.

Several limitations should be mentioned. This study presented only 3-PBA data, unlike previous NHANES and GerES IV pilot studies which have measured such PYR metabolite as cis- and trans-3-(2,2-dichlorovinyl)-2,2-dimethyl-cyclopropane-1-carboxylic acid (DCCA), 3-(2,2-dibromovinyl)-2,2-dimethyl-cyclopropane-1-carboxylic acid (DBCA) and 4-fluoro-3-phenoxybenzoic acid (F-PBA) in general populations. However, the NHANES study indicated that F-BPA and DBCA were less frequently detected in the general population (< 30% and < 50%, respectively); moreover, we found that DCCA measurement conducted in our laboratory was not as technically reliable as 3-PBA measurement. Second, creatinine-correction of urinary metabolites might overestimate the 3-PBA in women because urinary creatinine levels depend on the volume of muscle bulk. If so, the statistically significant difference in urinary 3-PBA levels between men and women may be misleading, and comparison of 3-PBA concentrations in the spot urine samples should be limited within a particular gender or age group.

In summary, despite one sample collection area and spot urine, the present study is the first to report that PYR metabolite 3-PBA measurement in urine was performed for a large general population and occupationally-exposed group in Japan. Our findings of a similar level of Japanese urinary 3-PBA to that in previous studies indicated that the level of PYR exposure in people in Hokkaido is nearly equal to the level in the U.S. and

German populations.

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