Occupational Leukoderma in Workers Engaged in 4-(p-Hydroxyphenyl)-2-Butanone Manufacturing

Yoshiharu Fukuda, Megumi Nagano and Makoto Futatsuka

Department of Public Health, Kumamoto University School of Medicine

Abstract: Occupational Leukoderma in Workers Engaged in 4-(p-Hydroxyphenyl)-2-Butanone Manufacturing: Yoshiharu Fukuda, et al. Department of Public Health, Kumamoto University School of Medicine—Occupational leukoderma was found to be caused by exposure to depigmentation agents. This is the first report associated with the depigmenting activity of 4-(p-hydroxyphenyl)-2-butanone and its crude products. The purpose of this paper is to present three cases of occupational leukoderma in the upper extremities of workers engaged in the manufacturing of 4-(p-hydroxyphenyl)-2-butanone. Two workers had symptoms of dermatitis in the same areas before depigmentation. An epidemiological study, their clinical courses and results of phototesting suggest that these cases of leukoderma were due to exposure to 4-(p-hydroxyphenyl)-2-butanone and its crude products.

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Key words: Occupational leukoderma, Depigmentation, Alkylphenol, 4-(p-hydroxyphenyl)-2-butanone, Raspberry Ketone

Since the first report by Oliver et al.1), occupational leukoderma due to phenol, catechol and hydroquinone compounds has been well documented2–9). Most of these compounds were found to have depigmenting activity and selective toxicity to melanocytes in in vivo and in vitro studies10–14).

The authors saw three cases of occupational leukoderma among workers engaged in the manufacturing of 4-(p-hydroxyphenyl)-2-butanone (HPB), known as Raspberry Ketone (RK). HPB is the crystallized form of a compound similar to alkylphenol but it contains monoketone in its molecule (Fig. 1). It is used commercially as a flavoring agent. There is no report in the literature associated with HPB-induced depigmentation. The purpose of this report is to describe the clinical courses, exposure conditions and the background of several incidents of leukoderma, and to discuss the toxicity of HPB.

Working Conditions and Epidemiology

Working conditions: The HPB manufacturing process in the workshop is shown in Fig. 2.

HPB is synthesized with acetone, formaldehyde and phenol by a two-step reaction. After the phenol is recovered, the distilled material is poured into vessels and dried to get an impure solid of HPB. The crude product is called Distilled RK (DRK). DRK is crushed and dissolved with a solvent. After the solvent is recovered, the filtered material is crystallized. In the refining step, the remaining material is recovered and reprocessed. The reused material is called Recovered RK (RRK). Finally, the product is dried and packed into 25 kg bags. In 1990, the workers engaged in the drying and packing process worked in a closed, hot room which had an area of 100 m² and they packed about 100 kg HPB a day. The purity of the final product is 99.98% and that of DRK is 90.99%, and DRK includes ten chemicals, whose maximum concentrations are shown to be 1.1% by gas chromatography-mass spectrometry (GC-MS) assay. The chemical structure of phenol (=0.3%) and four impurities were identified, but their characteristic and toxicity were not established.

The solidification process and the final process were done as open processes, but the others were closed. The chemical substances with which workers might come into contact in the open processes were the splashing of liquid

![Chemical structure of 4-(p-hydroxyphenyl)-2-butanone (HPB).](image)

Fig. 1. Chemical structure of 4-(p-hydroxyphenyl)-2-butanone (HPB).
in the first solidification process and the crystal in the final process, though the workers wore protective gloves and face masks in these processes.

Epidemiology: The HPB manufacturing at this plant had been carried out experimentally or on a small scale commercial basis from 1978 to 1989. After 1990, new investment was made, the production was increased annually and the number of workers was increased. The production of HPB in 1978 was 10 t/year, that in 1990 was 31 t/year and that in 1991 was 50 t/year.

Of 24 males engaged in the manufacturing process, we were able to investigate in 1994 the working conditions and symptoms of dermatoma in 22 workers in interviews and medical records. Nine of 13 workers who may have been exposed to chemical substances had some symptoms of dermatitis, such as itching, erythema, edema or vesicle formation. In most cases the dermatoma became more severe in the sunshine of spring and summer. These incidents occurred between 1986 and 1990, which coincided with the period when the HPB production increased.

The result of the epidemiological study is shown in Table 1.

Case Reports

Case 1. Male, 56 year-old

He had been engaged at this workshop since 1986. After a few months, itching, edematous and scaly erythema arose in his hands, forearms and wrists for about 6 months. These symptoms became more severe in the sunshine. After disappearance of the dermatitis, depigmentation spots were noted on the backs of his hands and the flexion sides of his wrists (Figs. 3, 4). The depigmentation spots on his hands were surrounded by hyperpigmentation. He retired from the company in 1990.

When he went to a hospital in December 1992, he was in good general condition, and no abnormal data were observed in urine and blood examinations. External applications of a mild corticosteroid ointment were continued for about one year. Although repigmentation gradually occurred, depigmentation was not completely eliminated.

Case 2. Male, 35 year-old

He has been engaged at this workshop since 1987. After a few months, itching and edematous erythema arose in his fingers, hands and wrists. The symptoms became more severe in the sunshine.

After disappearance of the erythema, depigmentation spots with hyperpigmentation were noted on his fingers and at the flexion side of his right wrist (Fig. 5). Several more rice-sized depigmentation spots appeared on his face, neck and chest.

When he went to a hospital in June 1992, he was in good general condition, and no abnormal data were observed in urine and blood examinations except for slight leukocytosis (9,100/mm³). Although no treatment was given, depigmentation spots on face, neck and chest had almost completely disappeared, while those on the wrists recovered slightly.

Case 3. Male, 36 year-old

He has been engaged at this workshop since 1989. In 1990, depigmenting spots, less than coin size, were noted on the flexion sides of his wrists and on his left thumb. He had no symptoms of dermatitis before depigmentation.

At his first visit to a hospital in June 1992, he was in good general condition and no abnormal data were observed in urine and blood examinations except for slight leukocytosis (9,100/mm³). Although no treatment was given, depigmentation spots showed improvement.

Phototesting: We performed phototesting on Cases 2
Table 1. Epidemiological study of work history and symptoms of dermatoma in 1994

<table>
<thead>
<tr>
<th>Work history</th>
<th>Exposure*</th>
<th>Dermatitis Symptoms$^3$</th>
<th>Photo$^2$</th>
<th>Depigmentation</th>
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<tr>
<td>Began</td>
<td>Duration (y)</td>
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<td>1977–</td>
<td>15</td>
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<td>1987–</td>
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*possible exposure to 4-(p-hydroxyphenyl)-2-butanone (RK) and/or its crude products.
$^1$ had symptoms of dermatitis; itching, edema, erythema and vesicles.
$^2$ suspected photosensitivity; symptoms of dermatitis became more severe in sunshine in spring and summer.

Fig. 3. Leukoderma in Case 1. After dermatitis, depigmentation spots (→) were noted on the backs of the hands of a 56-year-old male in 1992. The pigmentation spots were surrounded by hyperpigmentation.
and 3 in June 1995. The chemicals used were HPB crystal, 5% HPB in hydrophilic ointment, hydrophilic ointment and vaseline. Forty-eight hours after topical applications in pairs on their backs, ultra violet rays (270–320 nm; UVB) were applied to one side at a half of the minimal erythemal dose (MED) which had been measured beforehand. Forty-eight hours after the radiation, we evaluated the irritation reactions.

In Case 2, the spot where 5% HPB had been applied and irradiated with UVB showed a positive reaction: erythema. In Case 3, no reaction was noted at any spot.

Discussion

In 1939, Oliver et al. reported occupational leukoderma in workers engaged at a leather manufacturing company. These cases of leukoderma were induced by mono-benzyl ether of hydroquinone (MBEH) contained in rubber gloves. Hydroquinone and its compounds were later established to have depigmenting activity. In addition, several phenol and catechol compounds, para-tertiary butyl phenol (ptBP), ortho phenyl phenol (oPP), para-octyl phenol (pOP), 4-tertiary butyl catechol (4tBC) and others, were reported to have depigmenting activity.

Hydroquinone compounds are antioxidants used in the manufacture of such things as rubber, plastic and soluble oils, whereas phenol and catechol compounds are materials used in the making of rosins, dyes and other products. Leukoderma due to these compounds was almost completely limited to workers engaged in their manufacture. 4-(p-hydroxyphenyl)-2-butanone (HPB) is a compound similar to some of these depigmentation agents, but there are no reports associated with its depigmenting activity. It is possible that some chemicals containing in DRK and RRK influence to the development of depigmentation, but they do not contain the depigmentation agent established by the GC-MS assay.

In the present study, workers in the workshop where leukoderma occurred had contact with HPB in open processes because they wore protective rubber gloves which were not long enough to cover the elbow joints. The splashing of liquid material while pouring it into vessels in the first refining process was a possible source of contact, and the HPB crystal could possibly have been taken into the gloves during the drying and packing in the final process. As a result, chemicals could have remained inside the gloves for a long time, and the skin of their hands and wrists would have been exposed to a large enough dose to induce leukoderma. In Case 2, leukoderma occurred not only on the upper extremities but also on the face, neck and chest. Because the room...
where HPB was dried and packed was hot, he wore only an undershirt on the upper half of his body. Depigmentation spots on his face along the nasolabial fold suggested that HPB accumulated at the edge of his mask.

After these incidents, workers began to use longer gloves, washed their skin after working and several processes were improved; the solidification process was closed, exhaust fans and air-conditioners were installed, etc., so as to eliminate exposure to HPB. We failed to observe any new occurrences of depigmentation after these countermeasures were introduced by the company.

In two of the three cases of leukoderma, symptoms of contact dermatitis were present before the occurrence of depigmentation. In our epidemiological study, nine of 13 workers who were suspected of having been exposed to chemicals had some symptoms of dermatitis and they were more severe in sunshine or hot weather. These facts suggested that HPB and/or its crude products have irritant potency and phototoxicity and allergic contact dermatitis due to rubber gloves participated.

A supplementary event could be the positive reaction in the phototesting in Case 2. Although several depigmentation agents were found to irritate to the skin, there is no report of their phototoxicity.

With regard to phenol, cathechol and hydroquinone compounds resembling tyrosin in chemical structure, Bleehen et al. speculated that these agents interact with tyrosinase and/or other enzymes involved in melanogenesis. Some studies supported this hypothesis.

Recently, advances in research on melanogenesis, cell culture assays and development of antimelanoma agents have identified potential pigmentation-reducing agents. These studies suggested that depigmentation agents have a specific cytotoxic action on melanocytes except for a few agents which inhibit synthesis of melanine without cytotoxic action.

To evaluate the depigmenting activity, irritant potency and phototoxicity of HPB and its crude products, further investigations are required and we are studying HPB toxicity in vivo and in vitro with a view to the establishment of parameters for its safe usage.

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References