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The Excretion by Humans of the Phenol Derived *in vivo* from 2-Isopropoxyphenyl N-Methylcarbamate

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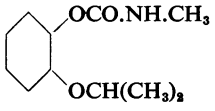
A method is needed for measuring the amount of insecticide absorbed by persons exposed to insecticidal spray in order to determine whether they have absorbed dangerous amounts of the toxicant. The expected course of degradation of the insecticide 2-isopropoxyphenyl N-methylcarbamate in vivo *by hydrolysis would be to give 2-isopropoxyphenol, which would then be excreted in the urine. A test for the presence of this phenol in urine would provide a method of checking exposure to the insecticide.*

Two methods for the determination of this phenol in urine are described in this paper.

By gas chromatography it is possible to examine the steam-volatile phenols present in acid-hydrolysed urine. Normal urine shows peaks corresponding to guaiacol, phenol and p-*cresol; the urine of persons who have taken small doses of 2-isopropoxyphenol and 2-isopropoxyphenyl N-methylcarbamate shows an extra peak corresponding to 2-isopropoxyphenol, and the excretion rate of guaiacol is slowed.*

This procedure may prove too complex for use in the field. The second part of the paper describes a simpler yet satisfactory colorimetric method of determination which requires only equipment generally available in a chemical laboratory.

In the course of the study of 2-isopropoxyphenyl N-methylcarbamate (I) as a potential insecticide it became necessary to devise a test which could be used to check the absorption of the pesticide by persons exposed to the spray or to sprayed surfaces. It was suggested at a meeting of a WHO Expert Committee on Insecticides that the laboratories of the Toxicology Research Unit, Medical Research Council, Carshalton, Surrey, England, and of the Tropical Products Institute, Department of Scientific and Industrial Research, London, should collaborate on devising quantitative methods for determining the metabolites of this insecticide excreted in urine.



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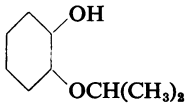

II

The expected course of degradation of the carbamate *in vivo* by hydrolysis would be to give 2-isopropoxyphenol (II), which would then be excreted in the urine, probably as the glucuronide. A test for the presence of II in urine would thus provide a simple method of checking exposure to the insecticide. The Tropical Products Institute has studied the phenol (II) content of urine by gas chromatography, while the Toxicology Research Unit has examined a colorimetric method for the estimation of the phenol in urine that can be used for surveillance of persons exposed to the insecticide. The results of these investigations are given below.

I. DETERMINATION BY GAS CHROMATOGRAPHY [4]

EXPERIMENTAL

Urine normally contains appreciable and variable amounts of phenol derivatives. Of the phenols produced by hydrolysis of the urine only a few are volatile in steam so that distillation of the acidified urine achieves a useful separation. The work at the

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[4] This part was written by J. A. Dawson, E. M. Thain & J. B. Ward, Tropical Products Institute.

Toxicology Research Unit (see Part II below) has shown that the distillate also contains any 2-isopropoxyphenol originally present in the urine.

At the Tropical Products Institute samples of normal urine were subjected to hydrolysis and distillation; the phenols were extracted from the distillate with diethyl ether and a small aliquot of this extract was injected into a suitable gas chromatograph. Three major peaks were detected in the chromatogram with retention times corresponding to guaiacol, phenol and *p*-cresol, the *p*-cresol giving, in general, the largest peak.

Six male volunteers took small doses (92.2 mg) of 2-isopropoxyphenol by mouth at night. Urine samples were collected on rising and throughout the following day and night. When these samples were examined by gas chromatography an additional peak, with retention time corresponding to 2-isopropoxyphenol, was present.

Three subjects later took small amounts (50 mg) of the carbamate. Urine samples were collected and examined as before and the chromatograms were found to contain the peak corresponding to 2-isopropoxyphenol.

The recovery of 2-isopropoxyphenol was checked by adding known amounts of the phenol to " blank " urine samples: the recovery, determined colorimetrically, was 98.5%.

METHOD

An aliquot (100 ml) of the urine sample was diluted to 150 ml and acidified with concentrated hydrochloric acid (15 ml). The urine was refluxed for 30 minutes and then distilled until 100-120 ml distillate had been collected. The distillate was extracted with diethyl ether (3 × 50 ml) and the extract concentrated to 10 ml (or 2 ml in the case of the normal urine samples). A small portion (0.5 μl) of the ethereal solution was injected into the gas chromatograph.

Calibration curves were prepared for the phenols under question which related weight of phenol placed on the column to either the area under the peak or peak height. These curves were then used for measuring the concentrations of phenols present in urine.

The instrument used was a Pye Argon Chromatograph with a 125 × 0.4-cm glass column packed with 100-120-mesh glass beads (" Ballotini ") supporting 0.2% by weight of tri-(2,4-xylenyl) phosphate. The column temperature was 110°C, argon flow-rate 40 ml per minute, and detector voltage 1750 volts.

RESULTS

The chromatographic conditions described above gave the following retention times:

Guaiacol: 5 minutes
2-Isopropoxyphenol: 6 minutes
Phenol: 11 minutes
p-Cresol: 18 minutes.

Samples of urine from five volunteers were examined: the retention times of the major peaks in the chromatograms of these control samples corresponded to guaiacol, phenol and *p*-cresol, the latter normally giving the largest peak, indicating about 10-20 times as much *p*-cresol as guaiacol or phenol. Several minor peaks were also present in the chromatograms of the normal samples but no attempt was made to identify them.

One overnight control sample from one subject gave rise to a very large peak with a retention time of 26 minutes. The person concerned had, the previous evening, eaten a spiced meat dish flavoured with cloves and bay leaves; it was found that eugenol, the major constituent of clove oil, when chromatographed under the same conditions, also had a retention time of 26 minutes.

Figures for the normal concentration of guaiacol and phenol in urine are given in Table 1. This table also gives the " 2-isopropoxyphenol equivalents " of the guaiacol and phenol concentrations; these have been calculated assuming that, in the colorimetric method for the determination of phenols used by the Toxicology Research Unit (see below), the molar extinction coefficients of guaiacol, phenol and 2-isopropoxyphenol are approximately equal. As guaiacol and phenol are the compounds primarily responsible for the colour developed from control samples of urine, then the sum of the two " 2-isopropoxyphenol equivalent " figures will give the approximate apparent 2-isopropoxyphenol content of the controls. These totals are also listed in Table 1; the mean is 8.9 μg/ml with a standard deviation of 5.5 μg/ml.

Similar figures for the guiacol and phenol content of urine at different times after taking doses of 2-isopropoxyphenol and 2-isopropoxyphenyl N-methylcarbamate are given in Tables 2 and 3 respectively. Table 4 gives corresponding figures for the 2-isopropoxyphenol content of urine at different times after taking doses of the phenol and 2-isopro-

TABLE 1
EXCRETION OF GUAIACOL AND PHENOL: CONTROL SAMPLES

Subject	Guaiacol (μg/ml)	Phenol (μg/ml)	2-Isopropoxyphenol equivalents		
			Guaiacol [a]	Phenol [a]	Guaiacol + Phenol [a]
A	1.7	0.6	2.1	1.0	3.1
	0.4	1.6	0.5	2.6	3.1
	0.1	1.4	0.1	2.3	2.4
B	1.9	8.1	2.3	13.1	15.4
	2.3	10.0	2.8	16.2	19.0
	1.1	6.1	1.4	9.9	11.3
C	1.0	1.0	1.2	1.6	2.8
D	0.9	4.4	1.1	7.1	8.2
	1.6	2.3	2.0	3.7	5.7
	0.8	3.1	1.0	5.0	6.0
E	1.5	7.1	1.8	11.5	13.3
	3.0	5.6	3.7	9.1	12.8
	1.7	6.4	2.1	10.4	12.5
			Mean:		8.9
			Standard deviation:		5.5

[a] Expressed as μg 2-isopropoxyphenol per ml.

poxyphenyl N-methylcarbamate. Also given in this table are figures for the recovery of 2-isopropoxyphenol after taking doses of the two compounds. These figures show that only about 30% of the phenol derived from the carbamate is recovered from the urine and that the majority of this—approximately 90%—is excreted within about eight hours of taking the carbamate.

A summary of all these results is given in Table 5.

DISCUSSION

It is clear from Table 1 that the concentration of phenols (probably as glucuronides) in normal urine differs considerably from person to person and also from time to time. The mean concentration, expressed as 2-isopropoxyphenol, was found to be 8.9 μg/ml with a standard deviation of 5.5 μg/ml.

In addition to this natural variation it is apparent from Tables 2 and 3 that the excretion of guaiacol and phenol is affected by taking doses of both 2-isopropoxyphenol and 2-isopropoxyphenyl N-methylcarbamate, the concentration of guaiacol in urine being very considerably reduced during the 8-10 hours immediately following the ingestion of these compounds.

It must be noted that the control samples were obtained from adult males living on normal "English" diets. The presence of eugenol in the urine of a person who had eaten a clove-flavoured dish has already been mentioned; although eugenol itself is unlikely to react positively in the colorimetric method used by the Toxicology Research Unit, other phenols derived from various food sources may become a problem when dealing with the urine from people with different dietary habits.

Taking all these factors into account it is obvious that it is not possible to fix any reliable "blank" value which could be used to correct apparent 2-isopropoxyphenol contents, determined colori-

TABLE 2
EXCRETION OF GUAIACOL AND PHENOL AFTER TAKING 2-ISOPROPOXYPHENOL [a]

Subject	Guaiacol (μg/ml)	Phenol (μg/ml)	2-Isopropoxyphenol equivalents		
			Guaiacol [b]	Phenol [b]	Guaiacol + Phenol [b]
			First overnight sample		
A	ND	3.7	ND	6.0	6.0
B	ND	0.2	ND	0.3	0.3
C	Tr.	3.0	Tr.	4.9	4.9
D	Tr.	1.1	Tr.	1.7	1.7
E	2.0	8.7	2.5	14.1	16.6
F	ND	1.9	ND	3.1	3.1
Mean					5.4
			Following day sample		
A	Tr.	4.0	Tr.	6.5	6.5
B	Tr.	7.0	Tr.	11.3	11.3
C	2.6	2.9	3.2	4.7	7.9
D	Tr.	1.0	Tr.	1.6	1.6
E	3.4	2.3	4.2	3.7	7.9
F	Tr.	4.1	Tr.	6.6	6.6
Mean					7.0
			Second overnight sample		
B	0.8	5.4	1.0	8.8	9.8
D	0.7	0.5	0.9	0.8	1.7
E	4.7	15.1	5.8	24.5	30.3
F	1.0	4.1	1.2	6.6	7.8
Mean					12.4

[a] ND = not detected; Tr. = trace.
[b] Expressed as μg 2-isopropoxyphenol per ml.

metrically, due to the positively reacting phenols present in normal urine.

Additional complications in the use of the colorimetric procedure for the estimation of the extent of exposure of an individual to 2-isopropoxyphenyl N-methylcarbamate became apparent from a study of the results given in Table 4. Of the doses of 2-isopropoxyphenol and the carbamate taken, only about 30% was detected in the urine as the phenol; of this fraction about 90% was excreted in the first 8-10 hours after ingesting the dose, with the remaining 10% excreted in the following 8-10 hours.

It is clear that the amount of 2-isopropoxyphenol found in a sample of urine can be related to the amount of carbamate entering the body only if the following information is available:

(*a*) the length of time during which the insecticide is ingested;

(*b*) the total volume of urine containing metabolites of the insecticide;

(*c*) the individual variation of the rate of excretion of 2-isopropoxyphenol with time after taking the 2-isopropoxyphenyl N-methylcarbamate;

(*d*) the individual factors relating the amount of carbamate ingested to the amount of 2-isopropoxyphenol excreted in the urine;

TABLE 3

EXCRETION OF GUAIACOL AND PHENOL AFTER TAKING 2-ISOPROPOXYPHENYL N-METHYLCARBAMATE [a]

Subject	Guaiacol (μg/ml)	Phenol (μg/ml)	2-Isopropoxyphenol equivalents		
			Guaiacol [b]	Phenol [b]	Guaiacol + Phenol [b]
First overnight sample					
B	ND	2.5	ND	4.0	4.0
D	Tr.	5.0	Tr.	8.1	8.1
F	Tr.	2.0	Tr.	3.2	3.2
Mean					5.1
Following day sample					
B	1.5	9.8	1.8	15.9	17.7
D	0.5	2.9	0.6	4.7	5.3
F	0.5	3.2	0.6	5.2	5.8
Mean					9.6
Second overnight sample					
B	0.8	10.0	1.0	16.2	17.2

[a] ND = not detected; Tr. = trace.
[b] Expressed as μg 2-isopropoxyphenol per ml.

TABLE 4

EXCRETION OF 2-ISOPROPOXYPHENOL [a]

Subject	Urine content (μg/ml)			Fraction of dose (%)			
	First overnight	Following day	Second overnight	First overnight	Following day	Second overnight	Total
After taking 2-isopropoxyphenol (92.2 mg)							
A	57.8	5.0	—	30.7	4.9	—	35.6
B	40.0	16.0	ND	26.0	3.7	ND	29.7
C	37.6	3.9	—	44.4	1.7	—	46.2
D	39.0	6.0	ND	16.0	5.4	ND	21.5
E	136.7	15.5	5.2	44.4	4.4	2.1	51.0
F	88.0	8.9	ND	39.6	4.2	ND	43.8
Mean	66.5	9.2		33.5	4.0		38.0
After taking 2-isopropoxyphenyl N-methylcarbamate (50 mg) [b]							
B	17.6	3.0	Tr.	26.6	2.2	Tr.	28.8
D	21.1	1.5	—	31.0	2.7	—	33.8
F	15.0	3.8	—	24.7	1.9	—	26.6
Mean	17.9	2.8		27.4	2.3		29.7

[a] ND = not detected; Tr. = trace.
[b] Equivalent to 36.4 mg 2-isopropoxyphenol.

TABLE 5
MEAN VALUES FOR EXCRETION OF PHENOLS: [a] SUMMARY OF RESULTS

	First overnight sample	Following day sample	Second overnight sample
Controls			
Guaiacol + phenol	Mean: 8.9		
	Standard deviation: 5.5		
After taking 2-isopropoxyphenol (92.2 mg)			
Guaiacol + phenol	5.4	7.0	12.4
Isopropoxyphenol	66.5	9.2	Negligible
After taking 2-isopropoxyphenyl N-methylcarbamate (50 mg) [b]			
Guaiacol + phenol	5.1	9.6	(17.2)
Isopropoxyphenol	17.9	2.8	Negligible

[a] Expressed as μg 2-isopropoxyphenol per ml.
[b] Equivalent to 36.4 mg 2-isopropoxyphenol.

(*e*) the effect on excretion of the mode of entry of the carbamate, e.g., by mouth, by adsorption through the skin, etc.

All these factors tend to limit the application of the colorimetric method for the determination of 2-isopropoxyphenol in urine to detect exposure of an individual to the carbamate. However, the method may still have considerable value, as can be shown by the following considerations:

1. From the figures given in Table 1 it is probable that only one normal urine sample in a thousand will have an apparent 2-isopropoxyphenol content greater than 31 μg/ml. (The Toxicology Research Unit quotes a value of 35 μg/ml; see page 133.)

2. The greatest volume of urine collected as an overnight (8-hour) sample was approximately 1000 ml. At 31 μg/ml this gives a total of 31 mg phenol or 42 mg carbamate.

3. Correcting for a recovery of approximately 27%, this represents an original dose of about 150 mg carbamate.

4. The LD_{50} for 2-isopropoxyphenyl N-methylcarbamate is of the order of 100 mg/kg so that even for a person weighing only 50 kg a dose of 150 mg represents only 3% of the LD_{50} figure.

Thus, if any apparent 2-isopropoxyphenol content of less than, say, 50 μg/ml of urine is rejected as insignificant, it is very unlikely that any grown person who has received, at most, a dose of 5% of the LD_{50} figure of 2-isopropoxyphenyl N-methylcarbamate will be overlooked in a check on exposure to the carbamate.

It must, however, be pointed out that this argument applies:

(*a*) only to urine samples taken in the 8 hours immediately following the ingestion of the carbamate;

(*b*) to persons weighing 50 kg or more. The lower body-weight of a child is, however, likely to be at least partially offset by a reduction in the rate of production of urine, an overnight sample being less than 1000 ml.

Finally it must be emphasized that the results quoted above relate to adult males living on an " English " diet; the urine of other peoples with quite different normal diets may show a different pattern of results from that described above.

II. COLORIMETRIC DETERMINATION [1]

Although the phenol derived from 2-isopropoxyphenyl N-methylcarbamate can be accurately determined in human urine by gas chromatography, a simpler procedure is required for routine determinations. Such a method is needed for measurement of the amount of the insecticide absorbed by spraymen and others coming into contact with the material, to determine whether they have absorbed dangerous amounts of the toxicant. A colorimetric method based on the estimation of 2-isopropoxyphenol in urine described in this part of the paper is satisfactory for this purpose.

As was expected from the known behaviour of carbamates and phenols *in vivo*, the insecticide is hydrolysed in man, and the phenol released is excreted in conjugated form, probably as the glucuronide (Best & Murray, 1962; Williams, 1959).[2] The

[1] This part was written by D. F. Heath & J. A. Rose, Toxicology Research Unit.

[2] It has been shown by the Tropical Products Institute (see Part I above) that in this instance about 30% of the phenol can be recovered from urine after ingestion of the phenol or carbamate.

problem was therefore to separate 2-isopropoxyphenol from the other phenols which are normally present in urine, so that less than 5% of these phenols would be recorded. Separation was achieved by distillation from acid solution, which released 2-isopropoxyphenol from its conjugate and separated it from most natural phenols, which are non-volatile. The most important volatile phenol is *p*-cresol (Siegfried & Zimmermann, 1911; Williams, 1959) and this was not recorded by the colorimetric test for phenols used (Ettinger et al., 1951).

MATERIALS AND METHODS

Reagents

Concentrated HCl.

N-NAOH.

Sodium carbonate buffer (0.1 g Na_2CO_3 anhydrous in 500 ml water).

4-Aminoantipyrine (0.5% w/v in buffer, filtered, and stored in the dark. For use, dilute 10 times with buffer.).

Potassium ferricyanide (4% w/v in buffer, filtered, and stored in the dark. For use, dilute 10 times with buffer.).

Universal indicator papers.

Apparatus

Simple distillation apparatus with Liebig's condenser.

Graduated 10-ml tubes, stoppered.

Spectrophotometer.

Procedure

To urine (2 ml) were added water (8 ml) and concentrated hydrochloric acid (1 ml). The mixture was distilled until the distillate, collected in a graduated tube, totalled 7 ml. Some results quoted were obtained on specimens refluxed for 10 minutes before distilling. Later work showed this was not necessary. The distillate was made slightly alkaline (pH 7-9 with N-NaOH, and made up to 10 ml. A portion (1 ml) was taken, and buffer (4 ml), aminoantipyrine (3 ml of diluted reagent), and potassium ferricyanide (2 ml of diluted reagent) were added in turn. The mixture was shaken, and the colour was determined against a reagent blank at 510 mμ. The colour was stable for several hours at 18°-20° C. In the final solution 1 μg/ml corresponds to 50 μg/ml in urine, and gives an optical density of 0.08 in a 1-cm cell.

Modifications

Aldridge (1954) found that if phosphate buffer (M15 Sorensen, pH 7.6) was substituted for carbonate buffer throughout, better pH control was achieved, and the aminoantipyrine reagent was more stable. In the present experiments the reagent was stable in carbonate buffer for a fortnight at 4°C; but the substitution might be necessary with other batches of aminoantipyrine.

The colour is very easily estimated by eye, as discussed below.

RESULTS

Ten samples of normal urine were taken from eight subjects, five male and three female. Estimated as 2-isopropoxyphenol, the concentrations found were 14.5 ± 4.5 μg/ml (average ± standard deviation). The results were unchanged when the urine samples were stored for three days at 4°C.

Two male subjects took about 100 mg of 2-isopropoxyphenol at night by mouth. Urine specimens were collected at rising, and again at midday. The same two subjects later took about 100 mg of the insecticide, purified, and gave urine specimens as before. The concentrations of 2-isopropoxyphenol found in their urine are shown in Table 6.

TABLE 6

EXCRETION OF 2-ISOPROPOXYPHENOL FROM TWO MALE SUBJECTS [a]

Compound taken	Subject	Dose (mg)	Concentrations in urine (μg/ml)	
			Morning specimen	Midday specimen
2-Isopropoxyphenol	G	114	122	43
	H	105	69	9
2-Isopropoxyphenyl N-methylcarbamate	G	116	102	40
	H	110	102	11

[a] The subjects took the compounds in water just before going to bed. Urine specimens were taken on the following day on rising and at noon.

DISCUSSION

The standard deviation of the controls, 4.5 μg/ml, is too high a fraction of the average, 14.5 μg/ml, to apply statistics reliably. It is, however, very unlikely that more than one in a thousand of this population would show control values above 35 μg/ml.

After dosing, the clearance from subject H was much faster than that from subject G (Table 6).

Both after doses of 100 mg of the phenol and insecticide, however, excreted concentrations of 2-isopropoxyphenol more than twice any value likely to be found by chance. The test is probably therefore sensitive to a dose of about 70 mg of insecticide—i.e., 1 mg/kg—providing a urine specimen is taken within 8 hours of the reception of the dose.

These conclusions will have to be confirmed on subjects using the compound, as the normal phenolic excretion may vary with diet and way of life. This has been discussed above in the first part of this paper.

The red colour produced appears on a yellow background from the reagent. Its intensity is easily judged by eye over the critical range by looking downwards through the coloured solution in an ordinary ½-inch test-tube held over white filter-paper. If the colour was developed in a solution containing 0.7 μg/ml (corresponding to 35 μg/ml in urine), exposure could be judged by comparing the colours developed from urine specimens with this, a deeper colour indicating exposure to the insecticide. Twelve laboratory workers could all distinguish by eye colours developed from urine which contained amounts differing by only 5 μg/ml in the critical range of 10-120 μg/ml. Alternatively, an equivalent comparator might be made. With this modification the procedure is very simple, and requires only equipment available in every chemical laboratory.

It must be remembered, however, that the criterion of exposure may be different for a different population, so that control values must be obtained on the population likely to be exposed; and that the excretion is very rapid, so that no abnormal levels of phenol will be recorded in urine unless specimens are taken within a few hours of absorption. A similar test has, however, been used successfully to measure exposure of men manufacturing and packaging a similar insecticide, 2-naphthyl N-methylcarbamate (Sevin), by estimating 2-naphthol excreted in the urine (Best & Murray, 1962).

The test is likely to be applicable to other phenyl carbamate insecticides providing the phenyl group is not substituted in the *para-* position. Phenyl compounds with *p*-chloro groups are an exception, as *p*-chloro groups are removed by the reagent.

RÉSUMÉ

Lors de l'étude de l'isopropoxy-2 phényl N-méthylcarbamate en vue de son emploi comme insecticide, il est apparu nécessaire de mettre au point un test destiné à mesurer l'absorption du pesticide par des personnes exposées au cours de la pulvérisation ou à la faveur de contacts avec les surfaces soumises à cette pulvérisation. L'on doit notamment s'attendre à une hydrolyse *in vivo* du carbamate, hydrolyse conduisant à la formation d'isopropoxy-2 phénol éliminé ensuite dans les urines, probablement comme glycuronide. La mise en évidence de l'isopropoxy-2 phénol dans l'urine constituerait un moyen simple d'authentification d'une exposition à l'insecticide.

Deux méthodes de détermination de ce phénol dans l'urine sont décrites, et leurs résultats discutés. La chromatographie gazeuse permet l'examen des phénols présents dans l'urine diluée et acidifiée et entraînés par la distillation. Dans l'urine normale l'on observe des pics correspondant au guaiacol, au phénol et au *p*-crésol. L'urine de sujets ayant absorbé par la bouche de faibles doses d'isopropoxy-2 phénol et d'isopropoxy-2 phényl N-méthylcarbamate montre un pic supplémentaire correspondant à l'isopropoxy-2 phénol, et l'excrétion du guaiacol et du phénol est ralentie. Mais cette méthode est trop compliquée pour être utilisée comme test de routine.

Une méthode colorimétrique, plus simple et pourtant satisfaisante, de maniement beaucoup plus aisé, est ensuite décrite par les auteurs. Elle est basée sur le dosage de l'isopropoxy-2 phénol dans l'urine et peut être effectuée dans tout laboratoire d'analyses chimiques. Pourvu que le prélèvement soit effectué dans un délai de quelques heures après l'absorption, elle fournit un moyen simple et rapide d'évaluation de l'exposition à l'insecticide.

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