

A comparison of different methods used to assess sensitivity to the taste of phenylthiocarbamide (PTC)

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(Received April 1980; revised June 1980; accepted July 1980)

Abstract. Four methods for assessing sensitivity to the bitterness of phenylthiocarbamide (PTC) and propylthiouracil (PROP) were compared. Good agreement was found among results from forced-choice detection thresholds, recognition thresholds, and category ratings of single stimuli. Testing by means of papers impregnated with these compounds led to a high incidence of false positive responses from insensitive subjects. Phenylthiocarbamide was a slightly better discriminator of sensitive from insensitive subjects than was propylthiouracil. Category ratings of the intensity of the antimodal PTC threshold concentration are a valid, reliable and efficient screening method. Relative safety in the use of PTC and PROP is discussed.

Introduction

Individuals differ in their sensitivity to the bitter compound, phenylthiocarbamide (PTC) and to related compounds containing the functional group $N-C=S$ (Fox, 1932; Kalmus, 1971). Sensitivity to the taste of PTC is largely determined by genetic factors. Insensitive individuals possess a pair of recessive genes for this simple Mendelian characteristic (Blakeslee, 1932). These differences are shown by a bimodal distribution of detection thresholds in the population. Individuals are usually classified as sensitive "tasters" of PTC if their detection threshold lies in the concentration range below the antimode of the population distribution, and are classified as insensitive "nontasters" if their detection threshold lies above the antimode (e.g., see Hall, Bartoshuk, Cain & Stevens, 1975).

In practice, many different methods have been used to classify PTC tasters and nontasters. Fox (1932) originally placed crystals of PTC directly on the tongue, a procedure now abandoned. The most widely used method has been the so-called Harris-Kalmus procedure for determining detection thresholds (Harris & Kalmus, 1949). In this method, subjects are presented with eight solutions to taste, four containing a given concentration of PTC and four containing water. The subject attempts to sort the water samples from those containing PTC. Concentrations are adjusted by a factor of two in subsequent trials until a concentration is found at which the subject fails to discriminate water from PTC. Variations of this method have included 1) the use of distilled water as a solvent rather than boiled tap water (Fischer, Griffin & Kaplan, 1963), 2) the use of an interstimulus rinse (Glanville & Kaplan, 1965), 3) the use of the odorless compound, propylthiouracil (PROP) rather than PTC (Fischer & Griffin, 1961), 4) plugging the nose with cotton to minimize odor cues (Lawless, 1979) and 5) using

a forced-choice procedure allowing only one tasting of each sample rather than ad lib sipping (Lawless, 1979).

Another widely used procedure in anthropological studies and in field-testing situations has been to present subjects with a piece of filter paper which has been impregnated with PTC (e.g., Parr, 1934). The paper is usually placed on the tongue and the subject is asked about the taste. This method has been criticized for producing unacceptable proportions of false negative responses (Azevedo, Krieger, Mi & Morton, 1965) and for limited agreement with classification of tasters by recognition thresholds (Hartmann, 1939). Davis (1978) used paper tests in which the concentration of PTC in which the paper had been soaked was varied. He also added a forced-choice aspect to the paper test by including a comparison to a plain piece of paper without PTC.

A rarely used method for assessing PTC sensitivity has been to present single concentrations of PTC (Lawless, 1979) or PROP (Fischer & Griffin, 1961). In these studies, a concentration near the antimode of the threshold frequency distributions was presented with the expectation that nontasters would find the sample tasteless and tasters would find it very bitter. This insight is supported by experiments on the scaling of PTC bitterness by PTC tasters and nontasters. For example, Hall et al. (1975) found radically diverging functions for PTC bitterness for the two groups. In this case, there may be a strong relationship between threshold measures of sensitivity and suprathreshold intensity ratings, a relationship that is not always the case (see Bartoshuk, 1978). Lawless (1979) found a bimodal distribution for category ratings of the intensity of .0001 M PTC.

Few studies have addressed the question of how these different testing procedures may affect the classification of tasters and nontasters (Hartmann, 1939). In order to assess possible differences in classification, a forced-choice modification of the Harris-Kalmus procedure, paper tests, and category ratings of single concentrations were compared in a within-subjects design. A fourth method, the measurement of recognition thresholds, was also included due to the suggestion that some insensitive nontasters may still be able to discriminate low concentrations of PTC from water on the basis of the sulfurous aroma (L. Bartoshuk, personal communication). To this end, all four methods also used propylthiouracil as well as PTC, since PROP is claimed to be odorless (Fischer, Griffin & Kaplan, 1963).

Method

Subjects

Thirty-two subjects, employees of the U.S. Army Natick Research and Development Command, volunteered to participate. Three subjects failed to complete all sessions and were dropped from the analysis. Twenty-six subjects were male, aged 19 to 46, and six were female, aged 21 to 36. Seventeen had previous experience in psychophysical experiments on taste, and all but two were familiar with food acceptance testing.

Stimuli

Stimuli consisted of solutions of phenylthiocarbamide (PTC) ranging from .000001 to .0056 M in 1/4 log steps (factors of 1.8), solutions of propylthiouracil (PROP) ranging from .00001 to .01 M in 1/4 log steps, and in the recognition experiment, solutions of .32 and .1 M sucrose, .32 and .1 M NaCl, .0001 M quinine sulfate, and .004 and .001 M citric acid. Demineralized water served as the solvent, the rinse and as blanks in the threshold conditions.

Stimuli for the paper tests were made by soaking filter paper in saturated solutions (approximately .01 M) of PTC or PROP, drying, then cutting into strips. All stimuli were presented at room temperature (approx. 21°C). Solutions were sipped from small plastic cups as 10 ml samples, and were expectorated into a waste container. Subjects rinsed before tasting each stimulus.

Procedure

Three sessions were run. In the first session, subjects received a paper test for either PTC or PROP, and then a forced-choice detection threshold was determined for that compound. In the second session, the paper test and detection threshold were run for the other compound. In the third session, recognition thresholds were determined, and category ratings of perceived taste intensity were made of two PTC and two PROP stimuli.

Paper tests. Subjects were given a piece of filter paper (approx. 4 cm²) which had been soaked in either PTC or PROP solutions and told to place it flat on their tongue. If they tasted nothing, they were instructed to place the whole paper in their mouth and chew it. Subjects were then asked to describe the taste of the paper in their own words. No descriptions were suggested.

Forced-choice thresholds. Starting concentrations for forced-choice detection threshold trials were first approximated by a method of limits. If the subject had reported that the paper tasted bitter, the first stimulus solution was .0001 M PTC or .00032 M PROP, depending upon which compound was tested in that session. Subjects were asked if the solution was bitter, tasteless, or if they were unsure. If unsure, that concentration was used in the first forced-choice trial. If the response was bitter, subsequent stimuli decreased in concentration 1/2 log-step until the response changed. If the first response was tasteless, subsequent stimuli increased in concentration. The concentration at which the response changed became the starting concentration for forced-choice trials. A similar method of limits was used with subjects who reported that the paper was tasteless, but their starting point was .001 M PTC or PROP, for this approximation.

In the forced-choice trials themselves, subjects were provided with eight cups, coded A-H, four containing a single concentration of PTC or PROP, and four containing demineralized water. Subjects tasted each cup once, rinsing before each. On an answer sheet, they circled the letters representing cups they considered to have a taste. After each trial, feedback was given. If the targets had been discriminated correctly, the concentration was decreased by 1/2 log-step on the next trial. If mistakes were made, the concentration was increased by 1/2 log-

step on the next trial. When performance changed from correct to incorrect (or vice versa), the concentration between the last two trials was tested. This provided a reasonable experimental session of about $\frac{1}{2}$ hour in length, but $\frac{1}{4}$ log-step accuracy in determining thresholds.

Recognition thresholds. Subjects were presented the following solutions as examples of sweet, salty, sour and bitter solutions, respectively: .32 M sucrose, .32 M NaCl, .004 M citric acid, and .0001 M quinine sulfate. Demineralized water (after a water rinse) was presented as an example of a tasteless solution. Subjects were informed that this was an experiment on identifying taste qualities. Next, they were given random sequences of .1 M NaCl, .1 M sucrose, .001 M citric acid and water to identify. Embedded in these sequences were PTC and PROP stimuli. The first PTC and PROP stimuli to be presented were concentrations at the previously determined detection threshold of that subject. Subsequent PTC and PROP stimuli increased in $\frac{1}{4}$ log-steps until two bitter responses were elicited for each compound, or until the highest concentration of that compound was reached. PTC and PROP stimuli occurred twice as frequently as NaCl, sucrose, citric acid and water stimuli. For example, in a set of eight trials, two PTC, two PROP and one of each of the other four stimuli would be presented, in a random sequence. Responses allowed were sweet, sour, salty, bitter, tasteless or other.

Category ratings. Subjects tasted two samples of .0001 M PTC and two samples of .00056 M PROP. They were rated for perceived taste intensity on an eight point scale ranging from 0 (no taste) to 7 (very strong taste). Subjects also recorded a word describing the taste quality.

Results

Paper tests. Classification of subjects by their responses to paper impregnated with PTC generally agreed with classification by forced-choice thresholds. One taster, so classified by threshold criteria discussed below, called the paper tasteless, and three nontasters called the paper bitter. For PROP, however, the agreement with forced-choice thresholds was poor. Eight of the fourteen nontasters responded to the paper as bitter, a false positive rate of 57%.

Forced-choice thresholds. Figure 1 shows the distributions of forced-choice thresholds for PTC and for PROP for the 29 subjects. The PROP distribution covered a smaller concentration range than the PTC distribution, 2.5 and 3.75 log units, respectively, with standard deviations of .59 and .97 log units. Fifteen subjects with thresholds less than $10^{-3.25}$ M PROP were assigned PROP taster status, and 17 subjects with PTC thresholds less than $10^{-3.75}$ M PTC were assigned PTC taster status (94% agreement between compounds). These values were chosen in consideration of previous literature (Kalmus, 1971; Fischer & Griffin, 1961). No differences were found between thresholds of persons tested on ascending and descending series of forced-choice trials (t-tests).

Category ratings. The distributions of category ratings for 10^{-4} M PTC and $10^{-3.25}$ M PROP are shown in Figure 2. As in the threshold distributions, the standard deviations were greater for PTC than for PROP, 2.7 vs. 2.4 rating scale

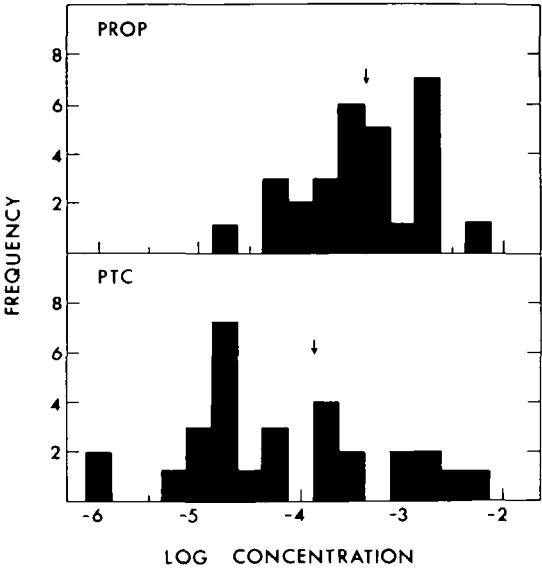


Fig. 1. Distributions of detection thresholds as determined in the forced choice procedure for PTC and PROP. Arrow indicates category boundary dividing tasters from nontasters.

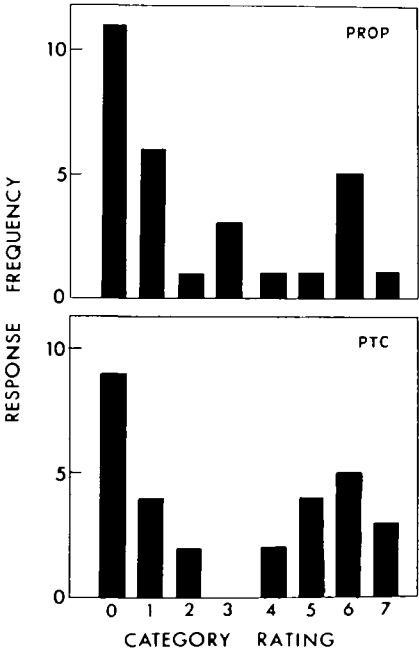


Fig. 2. Distributions of category ratings of perceived taste intensity of 10^{-4} M PTC and 10^{-3} M PROP. Each observation is the mean of two ratings by each subject (rounded down, 1.5 plotted as 1).

units. Good agreement was found between category ratings of perceived intensity and forced-choice detection thresholds. The rank order correlation of log PTC thresholds with ratings was $-.804$, and of PROP thresholds with ratings was $-.845$ ($p = .01$). Assignment of subjects with mean PTC intensity ratings higher than 3 to status as tasters produced 90% agreement with PTC threshold classification. Assignment of PROP taster status to subjects with mean PROP ratings higher than 1.5 produced 86% agreement with forced-choice classification. First and second ratings of these compounds were highly correlated, $r = .94$ for PTC and $.91$ for PROP, $p = .01$.

Recognition thresholds. Recognition thresholds were slightly higher than detection thresholds. The mean difference was $.28$ log units for PTC and $.13$ log units for PROP. The occurrence of higher recognition thresholds was more pronounced for PTC nontasters than for tasters (status assigned by detection threshold criteria), with mean differences of $.46$ and $.18$ log units (PTC). Nontasters also had an increased frequency of responses other than bitter and tasteless in their recognition threshold trials for PTC (32% vs. 8.3% for tasters) and for PROP (15% vs. 5%).

Method of limits. The first approximation of PTC and PROP detection thresholds by the method of limits differed from the final assigned detection thresholds by as much as 2 log units for PTC and 1.25 log units for PROP. For PROP, these differences were nonsystematic, while for PTC, subjects underestimated their sensitivity by $.24$ log units on the average ($t(28) = 2.05$, $p = .05$).

PTC and PROP. Three lines of evidence indicated that PROP was not as good as PTC for assigning taster status. First, variances in the detection threshold and category rating distributions were smaller for PROP than for PTC. Second, the mean distances of the taster and nontaster groups from the cutoffs in these distributions were smaller for PROP than for PTC. These mean distances were $.84$ log units for PTC and $.47$ log units for PROP in the threshold distributions ($t(28) = 3.12$, $p = .01$). In the category rating distributions these distances were 2.55 scale units for PTC and 2.02 units for PROP ($t(28) = 2.04$, $p = .05$). Finally, the percent agreement about taster-nontaster classification was generally better for PTC when comparing assignment across methods. The agreement was 93% for PTC and 83% for PROP between assignment by detection threshold and category rating criteria, 86% for PTC and 72% for PROP between assignment by detection thresholds and paper tests, and 76% for PTC and 55% for PROP between assignment by ratings and paper tests. This pattern of results persisted when other cutoffs for the taster-nontaster distributions were employed.

Discussion

No single method emerged as the unambiguous choice for PTC taster classification when the criterion was agreement with other methods. Even the forced-choice procedure differed from the majority of other methods over the classification of two subjects on PTC. However, several generalizations can be made.

First, there was good agreement among forced-choice detection thresholds, category ratings and recognition thresholds. The correlations among these methods are shown in Table I. When classification of tasters by the forced-choice detection threshold criteria is compared to classification by the category rating criteria for PTC and for PROP, unanimous agreement exists among the four methods for 75% of the subjects and agreement on three criteria for all but one subject. This agreement among methods emphasizes the robust nature of the PTC dimorphism.

Second, the category scaling task appears to be a potentially useful screening method. While suprathreshold judgments of intensity are not necessarily correlated with threshold measures of sensitivity (Bartoshuk, 1978) the category ratings for PTC and PROP antimodal concentrations were highly correlated with recognition and detection thresholds. The correlations (above .9) for first and second ratings of these stimuli offer evidence of reliability as well. The method is rapid and efficient, requiring no more than a few minutes in comparison to forced-choice threshold procedures which can last over a half hour. The method would appear especially useful for applications in which large groups of subjects are to be screened for PTC sensitivity.

Third, the fact that when comparing any two methods, a few subjects may fall into different groups, suggests that experimenters should consider using more than one test when assigning taster status in experiments with small groups of subjects. A nontaster can best be recognized by a constellation of effects: high detection and recognition thresholds, low ratings of the intensity of suprathreshold (re tasters) solutions, responding with taste qualities other than bitter or tasteless in recognition threshold trials, and occasional large differences between recognition and detection thresholds.

Caution is advised in the use of paper tests and the method of limits. Paper tests may result in high rates of misclassification. In contrast to the report of Azevedo et al. (1965), errors in the present study were those of nontasters responding to papers with reports of bitterness. Hartmann (1939), in the only within-subject comparison of methods, found both false positive and false negative responses to paper, relative to recognition thresholds. As shown in Davis's (1978) study, responses to paper may depend upon the amount of PTC present in the stimuli. Different recipes for the production of PTC papers could lead to different classification for the same individual. Finally, in the method of limits

Table I. Rank-order correlations among methods

	PROP Detection	PTC Rating	PROP Rating	PTC Recognition	PROP Recognition
PTC Detection	.837	-.804	-.718	.937	.770
PROP Detection		-.857	-.845	.810	.915
PTC Rating			.824	-.853	-.798
PROP Rating				-.759	-.787
PTC Recognition					.761

which is often used to estimate thresholds before the Harris-Kalmus procedure, subjects may underestimate or overestimate their sensitivity by a factor of 10 or more.

Choice of stimulus chemical poses problems. Three criteria have been considered in the choice of PTC or PROP, the question of odor cues, the degree of separation of tasters and nontasters, and the toxicities of the compounds.

As mentioned above, PTC was a better discriminator than PROP. In Figure 2, there is a clear antimode for PTC at rating 3, while for PROP, the dividing point is uncertain. Since the lack of a clear antimode for PROP might be due to a stimulus which was too weak, 25 of the subjects were recalled and asked to give category ratings of $10^{-3.0}$ M PROP. While the new distribution was bimodal, other difficulties arose. Two nontasters (by a majority of criteria) who rated the initial $10^{-3.25}$ M PROP stimuli as tasteless, now rated $10^{-3.0}$ M PROP as moderately strong. The classification of these subjects is unclear. The effect resembles the recruitment seen in the scaling of PTC bitterness by nontasters at high concentrations (Hall et al., 1975).

The availability of cues other than bitter taste for PTC is suggested by several results. First, two nontasters (by all other criteria) had PTC detection thresholds in the range of tasters. The contribution of olfaction is also consistent with the use of nonbitter responses by nontasters during PTC recognition threshold tests (especially the category "other") and the discrepancy between PTC detection and recognition thresholds for these subjects. The contribution of olfactory cues might be assessed by testing the detection thresholds of anomalous subjects while clean air is injected through the nose to minimize olfactory cues, and look for increases in detection thresholds (see Mozell, Smith, Smith, Sullivan & Swender, 1969).

Concern over the toxicity of these compounds has led to increased use of PROP in recent times, rather than PTC. These thiourea-related compounds have antithyroid properties. They inhibit the formation of thyroid hormone by inhibiting both the incorporation of iodide into organic form, and the synthesis of thyroid hormone from precursors (Gilman & Murad, 1975). As such, they can induce a hypothyroid state, observed both in experimental animals (Richter & Clisby, 1942) and in humans undergoing thiouracil therapy for hyperthyroidism (Astwood, 1945). While it has been claimed that PROP is less toxic than PTC (for example, see Fischer, 1967), no directly comparable data on human toxic manifestations exist.

Of the two compounds, more is known about adverse reactions to PROP due to its use in treatment of hypothyroidism. PROP is given orally in these therapies, in doses ranging from 100 to 900 mg/8 hrs, is concentrated in the thyroid, is rapidly eliminated from the body (plasma half life = 2 hrs), and is known to cross the placenta (Gilman & Murad, 1975). Adverse reactions to PROP therapy occur in about 3% of cases, mostly mild reactions involving skin rashes or gastrointestinal symptoms. In .44% of patients treated with PROP, major adverse reactions occur, involving depletion of white blood cells (mainly agranulocytosis) (Gilman & Murad, 1975). Martelo, Katmis & Yunis (1967) documented a case of bone marrow aplasia after 40 days of PROP therapy. Rapid recovery ensued

after discontinuation of the drug. Comparable effects with PTC have not been reported since it is not employed in treatment of thyroid disorders. However, a related compound, thiourea, caused similar toxic reactions, and allythiourea caused minor toxic reactions sufficient to discontinue its therapeutic use (Hercus & Purves, 1944).

Direct comparisons of toxicities of PTC and PROP are difficult to make because of differences in routes and schedules of administration. The lethal dose (single, oral) for rats cited in Merck (1960) is 40 mg/kg for PTC while the toxic substances list (DHEW, 1972) lists the lethal dose of PROP for rats as 90 mg/kg administered subcutaneously and repeatedly over 6 weeks. Caution is advised in generalizing rat toxicities to man. Species differences exist, and rats may be comparatively sensitive to thioureas and related compounds (Richter & Clisby, 1942; DHEW, 1972). For example, sulfonamides are active antithyroid compounds in the rat, but not in man (Trotter, 1962, p. 15).

Despite over forty years of taste testing with PTC without a reported mishap, some concern over toxicity appears warranted. A nontaster in a forced-choice detection threshold experiment could be exposed to 100-200 mg of PTC or PROP, and probably more in the traditional Harris-Kalmus procedure which allows ad lib sipping. Consumption of these amounts, however, entails the doubly conservative assumption that the subject swallows all the stimuli, and that this behavior goes undetected by the experimenter. Even though swallowing of stimuli is rare, and often grounds for dismissal from an experiment, sublingual absorption may occur. Sublingual administration of drugs is known to be an effective route for introduction of small polar molecules like nitroglycerin (Nickerson, 1975). Research on sublingual absorption of bitter compounds using radioactive labels may address this question. Screening methods such as the category scaling task with single solutions or recognition threshold procedures limit the subject's exposure to these questionably safe compounds.

Acknowledgements

This research was performed while the author held a postdoctoral associateship from the National Research Council, at the Behavioral Sciences Division of the Food Sciences Laboratory, U.S. Army Natick Research & Development Command. Support from these sources is gratefully acknowledged. Thanks are extended to Herb Meiselman for comments, Lawrence Digman for statistical assistance, and Judith A. Owens, M.D. for assistance with toxicology. Reprint requests should be sent to Harry Lawless, Monell Chemical Senses Center, 3500 Market Street, Philadelphia, PA 19104.

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