The solubility of clinically useful pentaerythritol tetranitrate (PETN) has been determined in water and saline utilizing the radioactive labeled compound. The solubility agrees with one of the two previously reported values. The synthetic work has been included.

Two vastly differing values for the solubility of pentaerythritol tetranitrate (PETN) have been reported. Desvergnes (1) found the solubility to be 100 mcg./ml., while Leslie (2) reported a value of 1.5 mcg./ml. When PETN labeled with 14C was prepared for an extensive biological evaluation, it became possible to re-evaluate this solubility problem and resolve this discrepancy. The older methods prepared for an extensive biological evaluation, it became possible to re-evaluate this solubility problem and resolve this discrepancy. The older methods would be high due to the ready solubility of the nitrate ion.

**DISCUSSION**

Essentially, the method was to equilibrate 5 mg. of PETN-1,2-14C with 5 or 15 ml. of water or saline, filter to remove colloidal material, then count an aliquot in a scintillation solution composed of 0.7% PPO, 0.03% dimethyl POPOP, and 100 Gm. of naphthalene adjusted to 1 L. with freshly distilled 1,4-dioxane. The counting efficiency was 69%, and each sample was corrected for quenching by the addition of benzoic acid-14C as an internal standard.

It was found necessary to use a 0.22-µ filter (Millipore) to remove the colloidal material completely. However, successive passes through similar filters removed material from solution. At these low concentrations, this phenomena is not unexpected (3–5). These results are shown in Table I.
The identity of the material in solution was established by repeatedly spotting the aqueous filtrate on a TLC plate with Silica Gel G as the adsorbent. This gave, after irradiation, a single radioactive spot at \( R_f = 0.71 \) using the system of DiCarlo et al. (6) and was identical to that of authentic PETN.4

Using a 1-ml aliquot, the solubility was determined from the following formula (Table I):

\[
solubility = \frac{\text{c.p.m.} \times \text{dil. factor} \times 1/\text{eff.} \times 1/\text{conversion factor} \times 1/0.72 \mu \text{c.}}{\text{mg.}}
\]

### EXPERIMENTAL

Although the synthesis of pentaerythritol-1-14C (PE) has been described by Trevoy and Myers (7) the author used essentially the procedure of Schurink (8), modified by bubbling 25 mmoles acetaldehyde-1,2-14C,4 into a suspension of 15 mmoles Ca(OH)\(_2\), 285 mmoles formaldehyde as a 37% aqueous solution, and 15.1 ml of water. After removal of the calcium as its sulfate, the filtrate was stripped and the oily residue dissolved in water and steam distilled until the distillate gave a negative test with chromotropic acid (9). The solution containing the crude PE-1,2-14C was stripped on an oil pump, and the resulting solid was triturated with 3 \( \times \) 5 ml absolute EtOH, to give 2.28 Gm. of crude PE-1,2-14C melting at 140-142°. This material was converted to the tetra-acetate (PETA) according to the method of Wiersma et al. (10). After removal of the first crop of PETA-1,2-14C, saturation of the aqueous HOAc solution with (NH\(_4\))\(_2\)SO\(_4\) and extraction with ether gave an additional crop of the tetra-acetate. The combined yield of 3.66 Gm. of PETA-1,2-14C, m.p. 76-77°, was dissolved in 55 ml of MeOH containing 3.66 ml of 86% formaldehyde as a 37% aqueous solution with (NH\(_4\))\(_2\)SO\(_4\) and extraction with ether gave an additional crop of the tetra-acetate. The solution containing the crude PETA-1,2-14C was washed with 1 ml of cold water added. After 30 min., the precipitate was filtered, and the crude PETN-1,2-14C was washed with 1 N NH\(_4\)OH, water, and absolute EtOH. Recrystallization from aqueous acetone containing a trace of Na\(_2\)CO\(_3\) gave 3.10 Gm. of PETN-1,2-14C, melting at 140-142°. This material gave a single radioactive spot on TLC with \( R_f = 0.7 \). Aliquots were counted in a scintillation solution of 0.4% PPO and 0.1% diMePOPOP in toluene and found to have a specific activity of 4.72 mc./Gm.

The pure PETN-1,2-14C was dissolved in acetone and diluted (1:7) with lactose (previously passed through a 200-mesh sieve) and the stable powder again passed through a 200-mesh sieve. The specific activity of this powder was 0.59 mc./Gm. The PETN-1,2-14C can be extracted quantitatively from this lactose powder by extraction in a Soxhlet with anhydrous ether for about 1 hr.

### REFERENCES