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Calibration & Use of a Capintec CAPTUS 3000 Portable Thyroid Uptake System for Iodine-125 Bioassay Measurements

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The Effects of Environmental Chemicals on Neuroendocrine Function: Mode and Mechanism for Adverse Outcomes

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Contributing Organizations: NHEERL, NCCT, NCSU

B·O·S·C HUMAN HEALTH PROGRAM REVIEW

RESEARCH TRIANGLE PARK, NORTH CAROLINA JANUARY 13-15 2009

RESEARCH & DEVELOPMENT

LTG 1 Poster 05

Science Questions

Can a strategy be developed that will provide the means to determine the neuronal/molecular targets for environmental toxicants that alter the hypothalamic/pituitary control of gonadal function?

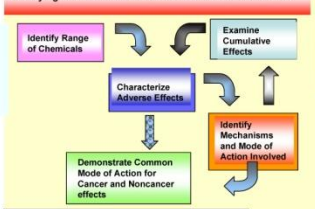
Research Goals

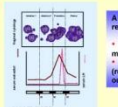
The hypothalamus and pituitary play critical roles in reproduction. In the female rat (and human), the mid-cycle (or ovulatory) surge of luteinizing hormone (LH) is a functional endocrine event that stimulates the final stages of follicular and oocytic maturation prior to ovulation. We have shown that environmental compounds from a variety of chemical classes are able to block this highly coordinated endocrine event. For example, the formamidine and dithiocarbamate pesticides block the catecholaminergic control of gonadotropin-releasing hormone (GnRH), and the chlorotriazine herbicides and intermediate metabolites affect the release of GnRH by a mechanism yet to be determined. We have also demonstrated that the disruption of the LH surge is a key event in the mode of action that leads to adverse reproductive outcomes including impaired pregnancy maintenance, impaired embryo development, reduced fertility, delayed puberty, premature reproductive senescence and mammary gland tumors in the female.

Due to the complexity of the observed toxicant-induced disruption of the neuroendocrine control of LH secretion and the numerous mechanisms that can be involved, we are developing a strategy to rapidly identify those cellular and molecular targets within the brain-pituitary that are affected by exposure to a test chemical. This strategy combines a series of in vitro (cell culture) and ex vivo (tissue perifusion, brain slices) procedures to identify the numerous mechanisms associated with the disruption of pituitary-gonadal and pituitary-adrenal function. We are coordinating our test chemical selection in order to integrate our results with those of the National Computational Center for Toxicology's ToxCast Research Program based on the NovaScreen® database). This approach will provide the information needed to determine the mode of action underlying the adverse effects of the chemical and provide the basis for across species comparisons. A related effort examines the extent to which toxicant-induced changes in the pituitary-adrenal axis contribute to alterations in reproductive physiology.

Identifying the Range of Chemicals

Effects of Environmental Agents on Neuroendocrine Function: Identifying Common Modes of Action and Adverse Outcomes





A number of xenobiotics disrupt the regulation of luteinizing hormone (LH).

- What are the causes [target organ(s), molecular sites]?
- What are the consequences (reproductive and non-reproductive outcomes)?

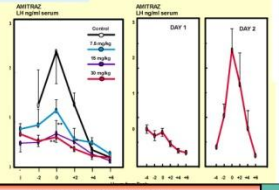
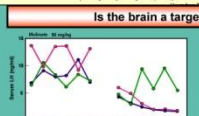


Table 1. Range of Chemicals That Modify the LH Surge

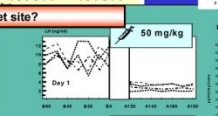
Formamidines	**Chlorotriazines**
Chlordimeform	Atrazine (+)
Amitraz	Propazine (+)
Diphenoxy Herbicides	Diaminochlorotriazine (+)
2,4-D (diphenoxy- (-) acetic acid)	Desethylatrazine (+)
	Deisopropylatrazine (+)
Thiocarbamates	Simazine (+)
Molinate	Amitryn (-)
Triallate	**Organophosphates**
Dithiocarbamates	Malathion
Thiram (+)	**Haloacetic Acids**
Metam Sodium	Dibromoacetic Acid
Ferbam	**Pharmaceuticals**
Sodium-Dimethyldithiocarbamate	Sodium Valproate
Organophosphate	Triclosan (-)
Malathion	**Pyrethroids**
	Permethrin
	Deltamethrin
	Cypermethrin
	Fenvalerate

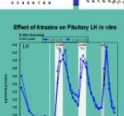
Red letters indicate positive effect on LH surge.
(+) effect or (-) no effect on onset of puberty.

Is the brain a target site?



Effects of molinate on the pulsatile release of LH in 3 ovariectomized rats. ↑ Attenuation of the pulses indicates the CNS mechanisms regulating gonadotropin-releasing hormone are changed.





Pituitary perifusion. Above, no differences in LH secretion between ex-vivo pituitaries of control or atrazine treated females. Below, there pituitary ACTH was not affected by atrazine when perifused in vitro

Effect atrazine or diaminochloro-triazine (100uM/24hr) on GnRH pulsatility in GT1-7 GnRH neuronal cells. ● Both chemicals inhibited the pulses indicating that GnRH neurons are sensitive to the chlorotriazines

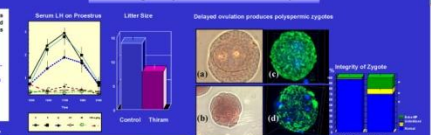
Characterizing Adverse Outcomes

Evaluating Ovarian Cycles using Vaginal Cytology

Metam Sodium Daily gavage with this dithiocarbamate induced a dose-related increase in persistent vaginal diestrus indicative of impaired ovarian function.

Estrous cyclicity is a required endpoint in standard multigenerational protocols. Importantly, for metam sodium, but not all LH-disrupting chemicals tested, the system adapts to the insult, indicating that for certain compounds the extended exposures commonly employed in toxicological testing would not identify more proximal alterations in reproductive activity.

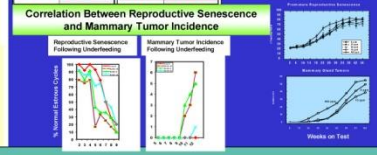
Evaluating Oocyte Function and Fertility



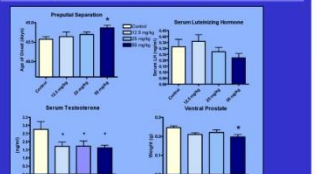
A single injection of the dithiocarbamate fungicide thiram, at 1500 h on vaginal diestrus disrupted estrous cyclicity, suppressed the LH surge and delays ovulation for 24 h. This delay in ovulation caused a reduced litter size.

Polyspermic zygotes exhibit an abnormal (Type II & III) pattern of cortical granule exudate suggestive of a relationship between abnormal cortical reaction and polyspermy in the delayed zygote.

Correlation Between Reproductive Senescence and Mammary Tumor Incidence



Evaluating Effects of Comp;ounds on Pubertal Develoment



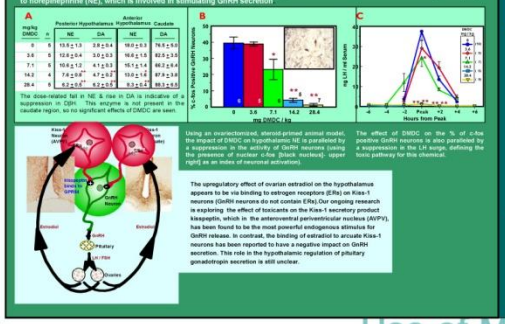
Effects of thiram on pubertal development in male rats. ● Altered hypothalamic catecholamines interferes with the secretion of luteinizing hormone and results in a decrease in testosterone release. This decreased testosterone results in delayed PPS and decreased growth of androgen-dependent tissues.

For effects of other chemicals on pubertal development, see Table 1.

Defining Toxicity Pathways

Dithiocarbamates

Compounds in this class of pesticides are metal chelators. In this case, sodium dimethyldithiocarbamate (DMDC) binds to the copper cofactor of the enzyme dopamine β-hydroxylase (DβH), suppressing the conversion of the neurotransmitter dopamine (DA) to norepinephrine (NE), which is involved in stimulating GnRH secretion



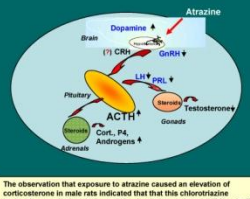
The dose-related fall in NE & rise in DA is indicative of a suppression in DβH. This enzyme is not present in the caudate region, so no significant effects of DMDC are seen.

Using an ovariectomized, steroid-primed animal model, the impact of DMDC on hypothalamic NE is paralleled by a suppression in the activity of GnRH neurons (using the presence of nuclear c-fos [block nucleus] upper right] as an index of neuronal activation).

The effect of DMDC on the % of c-fos positive GnRH neurons is also paralleled by a suppression in the LH surge, defining the toxic pathway for this chemical.

The upregulatory effect of ovarian estradiol on the hypothalamus appears to be via binding to estrogen receptors (ERs) on Kiss-1 neurons (GnRH neurons do not contain ERs).Our ongoing research is exploring the effect of toxicants on the Kiss-1 secretory product kisspeptin, which in the anteroventral periventricular nucleus (AVPV), has been found to be the most powerful endogenous stimulus for GnRH release. In contrast, the binding of estradiol to arcuate Kiss-1 neurons has been reported to have a negative impact on GnRH secretion. This role in the hypothalamic regulation of pituitary gonadotropin secretion is still unclear.

Is the stimulation of the HPA-axis and inhibition of HPG axis due to a common mode of action?

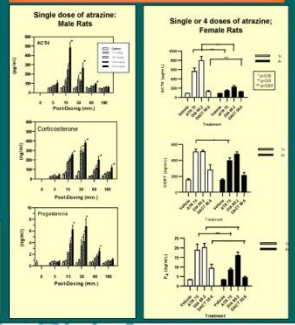


The observation that exposure to atrazine caused an elevation of corticosterone in male rats indicated that that this chlorotriazine herbicide was altering the hypothalamic-pituitary-adrenal (HPA) axis. This raised important questions that have been addressed:

- Are there dose-dependent changes in ACTH and Corticotropin Releasing Hormone (CRH)?
- Are the effects on the HPA mediated by a systemic or central MOA?
- Are the effects observed on the HPA and hypothalamic-pituitary-gonadal HPG) axis caused by a common mode of action?

Chlorotriazines

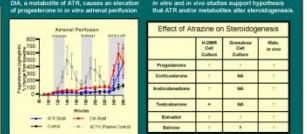
Atrazine stimulates dose and time-dependent increases in ACTH, corticosterone, and P4



Additional Evidence that Atrazine Alters Steroidogenesis

DIA, a metabolite of ATR, causes an elevation of progesterone in *in vitro* adrenal perifusion

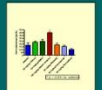
In vitro and in vivo studies support hypothesis that ATR and/or metabolites alter steroidogenesis.



Effect of Atrazine on Steroidogenesis

	H-295R Cell Culture	Granulosa Cell Culture	Male, in vivo
Progesterone	↑	↑	↑
Corticosterone	↑	NA	↑
Androstenedione	↑	NA	↑
Testosterone	±	NA	↑
Estradiol	↑	↑	↑
Estrone	↑	↑	↑

Not all Chemicals that Alter the LH Surge Induce Adrenal Activation



Is there a common MOA for cancer and noncancer effects?

ATR as a Model Compound

- Increased CRH alters NE and GnRH release and inhibits LH release.
- Increased CRH stimulates ACTH and adrenal steroid production (including E, androgens) that may lead to premature reproductive aging/mamary tumors. (Pending outcome of adrenal androgen study in rats.)
- Increased CRH also increases CNS dopaminergic activity resulting in decreased prolactin secretion.
- Increased DA may cause increased free radical production and damage to DA neurons (Ramirez et al., 2005).

Impact and Outcomes

By demonstrating that the brain is a target site for several new chemicals, we unveiled a new mode of action for consideration in reproductive risk assessment.

By establishing parallel dose-relationships among effects on hypothalamic catecholamines, GnRH neuronal activation and the LH surge in response to DMDC, our work has identified the toxic pathway for the adverse effect of this class of metal-chelating pesticides on female reproductive function.

Our research strategy enabled us to elucidate common (or disparate) modes of action of atrazine metabolites and other chlorotriazine herbicides, information that contributed to the assessment of the cumulative risks of this widely used class of compounds by OPP and OW.

In vitro and in vivo studies defining the effects of atrazine and metabolites on aromatase and steroidogenesis have been key for interpreting recent reports in the literature suggesting that the adverse effects of this compound are mediated by alterations in aromatase activity in cell lines and wildlife species.

Furthermore, this research has now identified perturbations in the hypothalamic-pituitary-***adrenal*** axis on the reproductive tract as new area of concern.

Future Directions

- Further identify the extent to which changes in the adrenal axis mediate the adverse effects of xenobiotics on reproduction.
- Characterize the extent to which the HPA may mediate selected chemical-induced developmental dysfunctions (e.g., pubertal development, blood pressure changes etc).
- Characterize toxic effects on the relationships among the neuroendocrine factors contributing to the hypothalamic secretion of GnRH.
- Collaboration with NCCT investigators, using their databases, to more rapidly :
  - identify the cellular mechanisms associated with altered neuroendocrine function, and
  - identify compounds for further evaluation of their effects on these two important neuroendocrine systems

Other Researchers Involved

Michael Narotsky, John Laskey, David Dix, Keith Hauk, Angela Buckalew, Michelle Hotchkiss, Ashley Murr

Contributors: NHEERL: Goldman; Fraites; Narotsky; Laskey; NCSU Collect of Veterinary Medicine: Zorilla, Tinfo; NCCT: Dix, Hauk

Use of Mechanistic Data in Risk Assessment

DIRECT AFFECTS OF ATRAZINE AND ITS METABOLITE DEISOPROPYL-ATRAZINE (DIA) ON PITUITARY AND ADRENAL HORMONE RELEASE USING *IN VITRO* PERIFUSION

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research and development

Abstract

Atrazine, a broad spectrum herbicide, is one of the most widely used herbicides in the United States, with current total annual use of approximately 76 million pounds of active ingredient. Previous work in our laboratory has shown that atrazine (ATR) and its metabolite deisopropyl-atrazine (DIA) are able to induce a dose-dependent increase in plasma ACTH, serum corticosterone (CORT) and progesterone (P4), at 15 and 30 min after a single oral administration *in vivo*. The mechanism for this increase in hypothalamic-pituitary-adrenal axis (HPA-axis) activation is currently unknown. To test whether ATR and DIA have a direct agonistic affect on the pituitary or adrenal glands, we conducted an *in vitro* perifusion, exposing pituitary and adrenal tissue to 50μM concentrations of either ATR or DIA during two twenty minute challenges over a three hour period. A positive control challenge was also used for both pituitary (10nM CRF) and adrenal (1nM ACTH) tissues, as well as a final challenge to test for viability of the tissue at the completion of the perifusion. Results indicate that ATR and DIA have no direct agonistic affect on pituitary or adrenal release of ACTH or CORT respectively, however treatment of adrenal tissue with 50μM DIA caused an approximate %100 increase over basal P4 release over the three hour perifusion, representing an increase from 3 pg/mg/min to 7 pg/mg/min at the 230min timepoint. While these results do not elucidate the mechanism by which ATR and DIA activate the HPA-axis after a single administration *in vivo*, increased release of P4 from the adrenal observed after *in vitro* treatment with DIA demonstrates a direct agonistic affect of the chemical on adrenal tissue, and one potential mechanism by which ATR and DIA are able to alter steroidogenesis and produce adverse reproductive outcomes *in vivo*.

Methods/Approach

Animals. For all experiments, male Wistar rats (60 days-old), obtained from Charles Rivers Laboratories, Raleigh, NC, and were housed 1 per cage under controlled temperature (20-24 C), humidity (40-50%) and light conditions (12h light/ 12h dark; lights on 0600) with Purina Laboratory Rat Chow (5001) and water available *ad libitum*.

Dosing solutions and procedures. For all experiments except the pituitary perifusion, rats were pre-dosed with vehicle (methyl cellulose) for 7 days to acclimate animals to handling and dosing. All dosing was conducted from 0700-0900 when both ACTH and corticosterone were at basal concentrations. Atrazine, DIA, or DACT (97.1% purity; a gift from Syngenta Crop Protection, Greensboro, NC) were prepared as a suspension in 1.0% methyl cellulose.

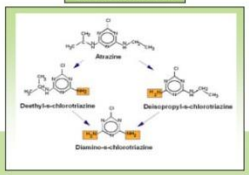
Hormone Experimental design. Groups (n=10) of animals were dosed with a single dose of 0 (vehicle), 5, 50, 100, or 200 mg/kg bw atrazine, 67.5mg/kg bw DACT, or 4, 10, 40, or 80mg/kg bw DIA by oral gavage in a volume of 5.0 ml dosing solution/ kg bw, and killed by decapitation 5, 15, 30, 60 or 180 minutes later. Plasma and serum were collected and frozen for the ACTH, progesterone, and corticosterone assays, respectively.

Pituitary and Adrenal Perifusion Experimental Design. The perifusion apparatus was set up as described in Goldman and Cooper 1993. Pituitary glands were removed and hemi-sected, while adrenal glands were quartered before placement in the perifusion apparatus. Treatment of the glands included two subsequent challenges with the test chemical, followed by one 60mM KCl,(pituitary) or 10μM ACTH(adrenal) challenge at the conclusion of the experiment to varify tissue viability. Perfusates were collected at 10min intervals and frozen for RIA analysis.

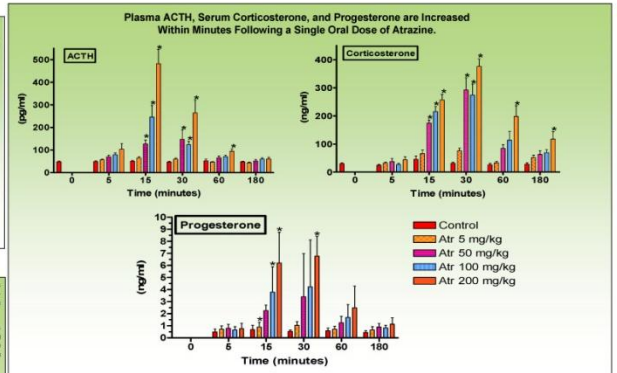
Radioimmunoassay. Serum and perifusion medium concentrations of corticosterone and progesterone were measured using coat-a-count radioimmunoassay kits obtained from Siemens (Los Angeles, CA). Plasma and perifusion medium concentrations of ACTH were measured using hACTH ImmuChem Double Antibody Kit, MP Biomedicals, LLC.

Statistical analysis. All hormone data were analyzed using ANOVA (General Linear Models (GLM); Statistical Analysis System (SAS), SAS Institute, Inc.). When significant ($p<0.05$) differences were indicated by ANOVA, the Dunnett Multiple Comparison Test was used to compare each treatment with the control within a given time point. Repeated measures ANOVA was used for analyzing perifusion data. When significant ($p<0.05$) differences were indicated by repeated measures ANOVA, Tukey Post Hoc Tests were used to compare test doses at each time point. All perifusion data was calculated at percent change from average baseline value measured in RIA concentration/ ml of sample/ mg of tissue/ min.

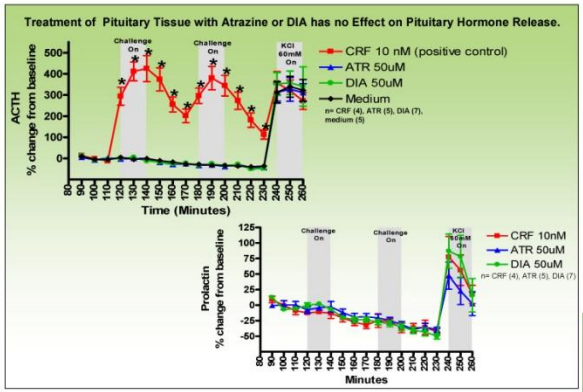
Atrazine Metabolism



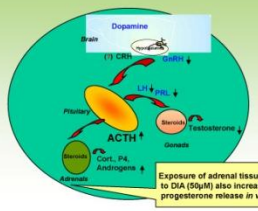
Plasma ACTH, Serum Corticosterone, and Progesterone are Increased Within Minutes Following a Single Oral Dose of Atrazine.



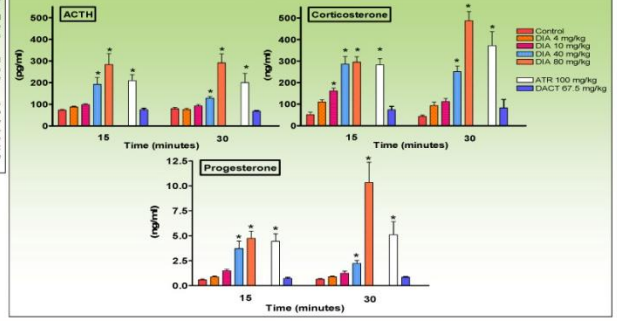
Treatment of Pituitary Tissue with Atrazine or DIA has no Effect on Pituitary Hormone Release.



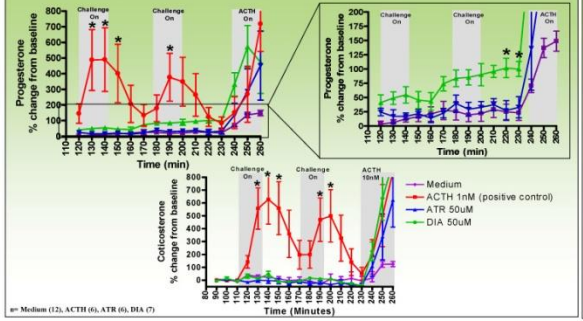
Effects of *In Vivo* Chlorotriazine exposure on the HPA and HPG axes



Plasma ACTH, Serum Corticosterone, and Progesterone are Increased Within Minutes Following a Single Oral Dose of DIA or Atrazine.



Treatment of Adrenal Tissue with DIA Causes an Increase in Progesterone Release, While Atrazine Does Not. Treatment with Atrazine or DIA had No Effect on Corticosterone Release.



Conclusions

***In Vivo* Studies:**

- **Dose-dependent increases in plasma ACTH, progesterone, and corticosterone were observed after a single oral dose of atrazine or DIA, with maximal increases in concentration observed at 15 or 30 minutes.**
- **HPA-axis activation was not observed after a single oral dose of DACT.**
- **It is unlikely that this HPA-axis activation is due to an acute stress reaction to the dosing procedure, given that animals were pre-dosed with vehicle for one week prior to administration of the test chemicals, and animals dosed with vehicle only did not display elevations in any hormone measured.**

***In Vitro* Studies:**

- **Perifusion experiments were conducted to examine potential direct effects of atrazine and DIA on pituitary and adrenal tissues.**

Pituitary Perifusion:

Neither atrazine (50μM) or its metabolite DIA (50uM) caused an increase in pituitary release of ACTH or prolactin at any time point.

Adrenal Perifusion:

Neither atrazine (50μM) or its metabolite DIA (50μM) caused an increase in adrenal release of corticosterone at any time point.

DIA (50μM) caused an increase in adrenal progesterone release (i.e. 220 and 230 min time points), while atrazine (50μM) did not alter adrenal progesterone release at any time point.

- **These data suggest that the changes in ACTH and adrenal steriods observed following a single oral dose of atrazine or DIA *in vivo* may be due to a CNS effect, or in the case of DIA, may be a combination of CNS effects and a direct effect of the chemical on adrenal tissue.**
- **Further studies are needed to determine how DIA may be able to modify steriodogenesis, potentially through effects on enzyme synthesis or function in this pathway.**

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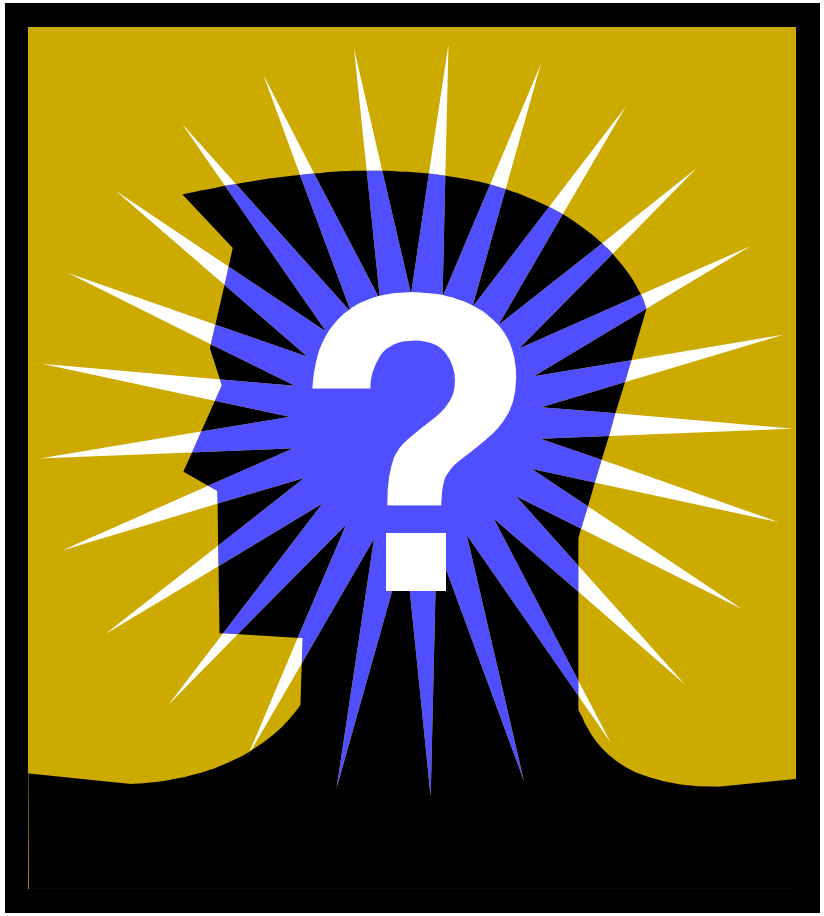
Capintec CAPTUS 3000 Portable Thyroid Uptake System

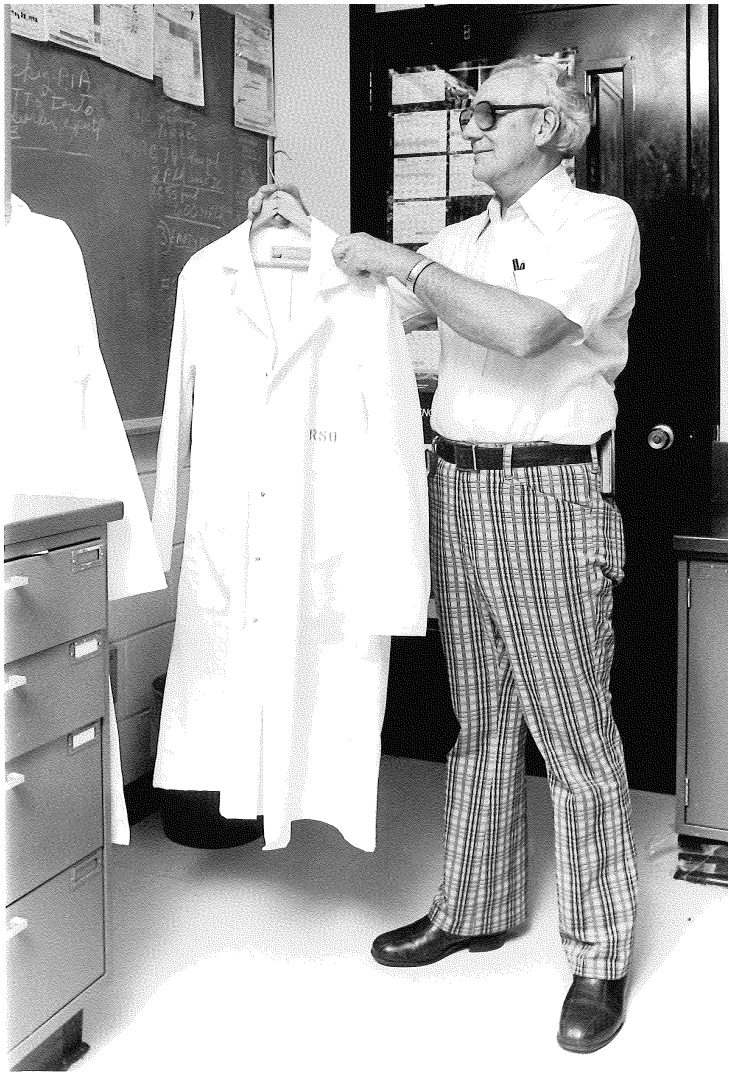
Statement of the Problem



While I still enjoy '80s music videos on VH1 Classic, using a system / method purchased in 1985 was no longer desirable.

Graham Hair, EPA/RTP RSO 1973-1994

Agreements for bioassay measure-ments at other institutions like Duke University and NIEHS no longer feasible.



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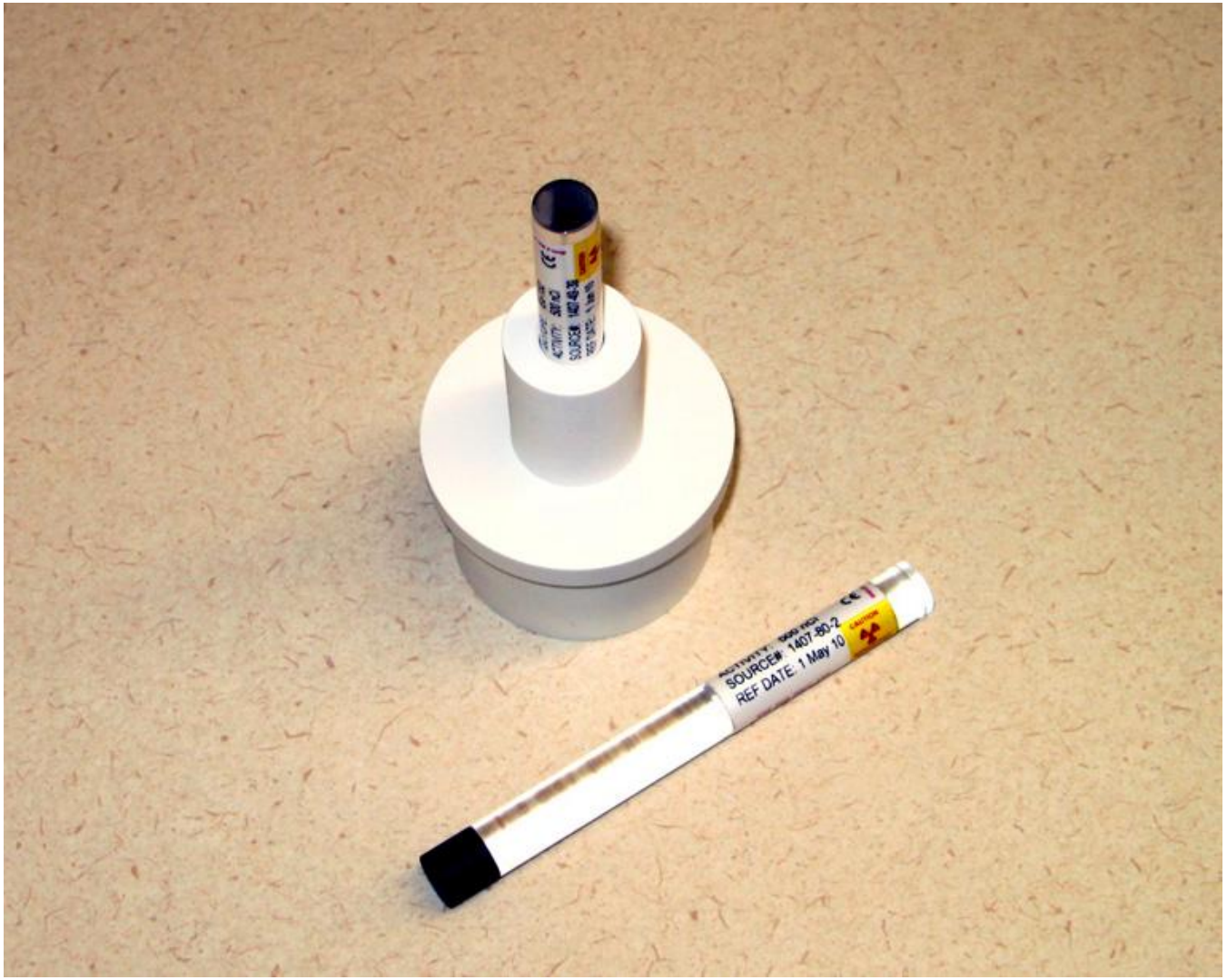

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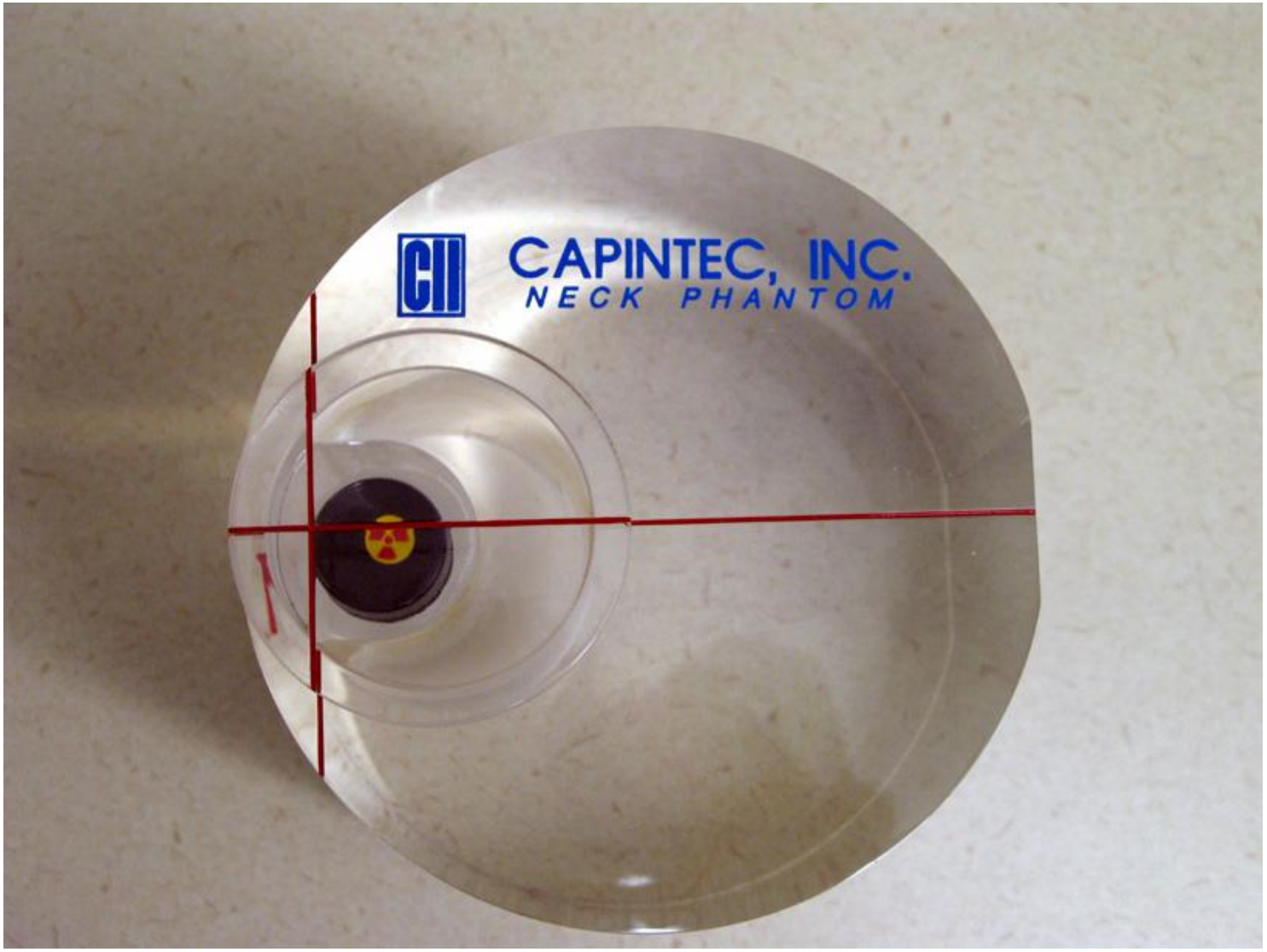

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Objectives

- Review Iodine-125 bioassay requirements
- Review Iodine-125 detection options.
- Review techniques to determine Iodine-125 efficiency.
- Discuss materials, methods and data observations.
- See the practical results of the calibration.

External Monitoring

- Whole Body (Badge) Monitoring
  - Higher energy beta emitters; photon emitters

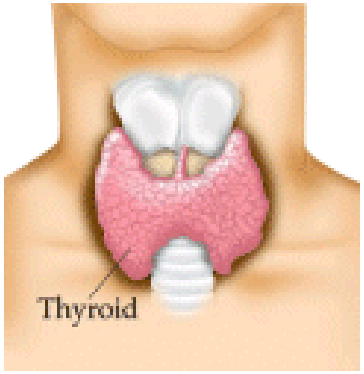
    Examples – P-32, Cr-51, I-125, As-73

- Extremity (Ring Badge) Monitoring
  - Higher energy beta emitters
    - Examples – P-32, P-33

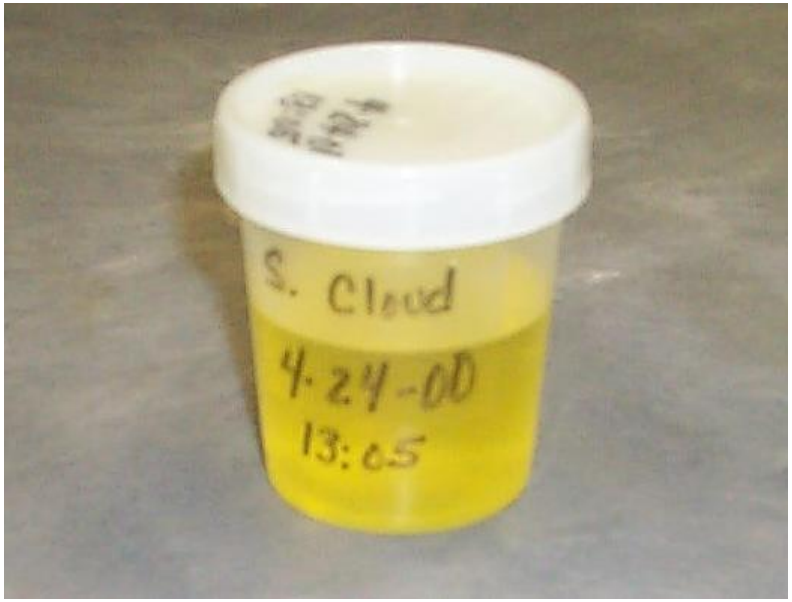
Picture Credits: Landauer Corp.

ldrsolutions.landauerinc.com

Internal Dose Assessment



Thyroid Scan
for I-125 & I-131



Urine Analysis
for H-3, C-14, P-32, & S-35

Picture Credit: (Thyroid gland)
http://www.uos.harvard.edu/ehs/radsafety/pur_i125.shtml

10 *CFR* 20 Limits on Intake

- Allowable Limit on Intake (ALI):
  - Inhalation: 40 µCi
  - Ingestion: 60 µCi

- Derived Air Concentration (DAC): 3×10^{-8} µCi/mL

But what about thyroid burden?

- Follow-up required for > 0.12 µCi from Reg. Guide 8.20

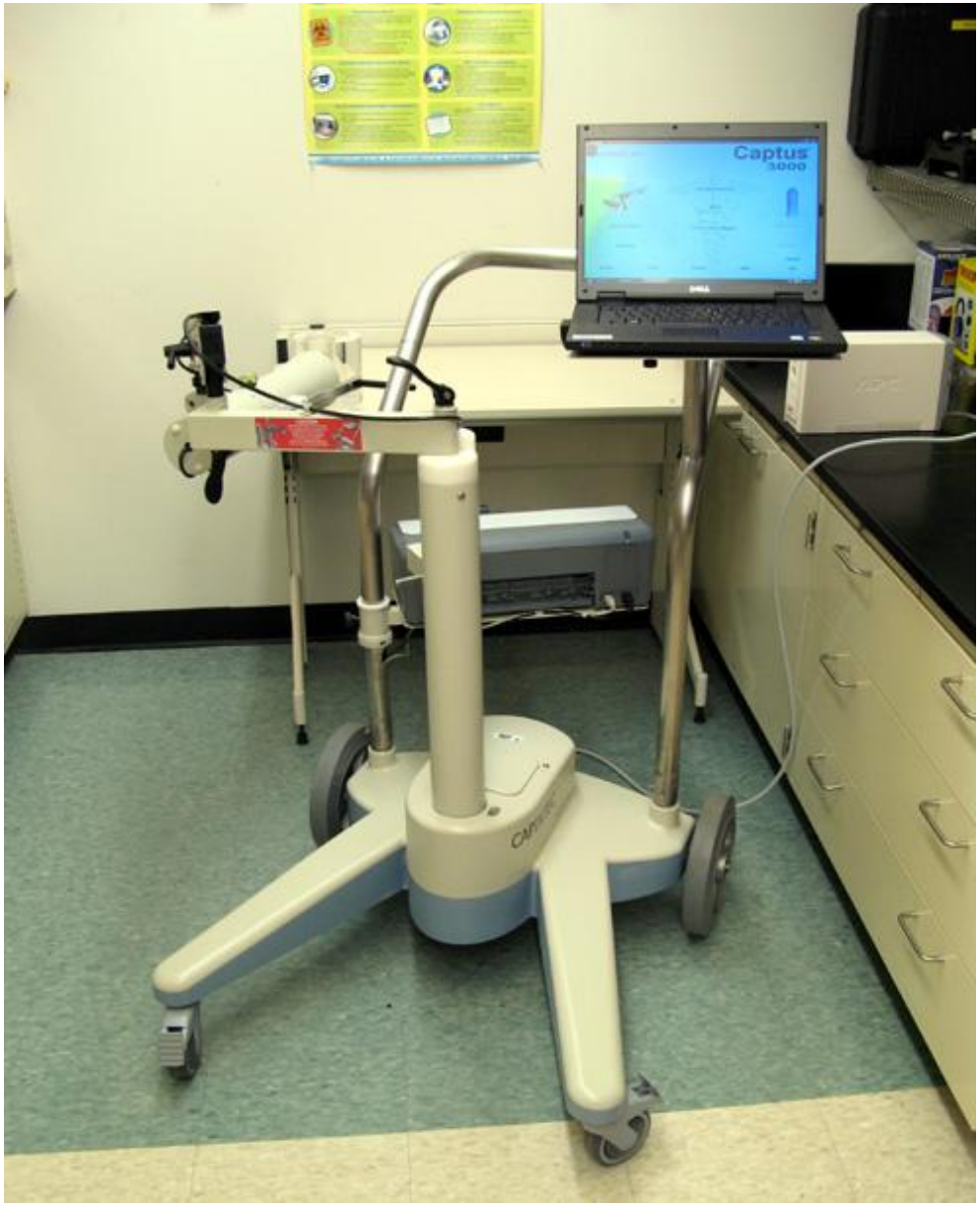
Internal Exposure Monitoring

TABLE 1
Activity Levels Above Which Bioassay
for I-125 or I-131 Is Necessary

Isotope	Activity Limit** (mCi)	
	Volatile or Dispersible	Bound to Non-Volatile Agent
^{125}I	1.0	10

**Activity Limit applies to the larger quantity:
[1] Three Month usage/disposal or
[2] Maximum activity handled at one time.

Reference: (Adapted)
U.S. Nuclear Regulatory Commission Regulatory Guide 8.20,
"Applications of Bioassay for I-125 and I-131," September, 1979.



Configured for Calibration / Spectrum Acquisition

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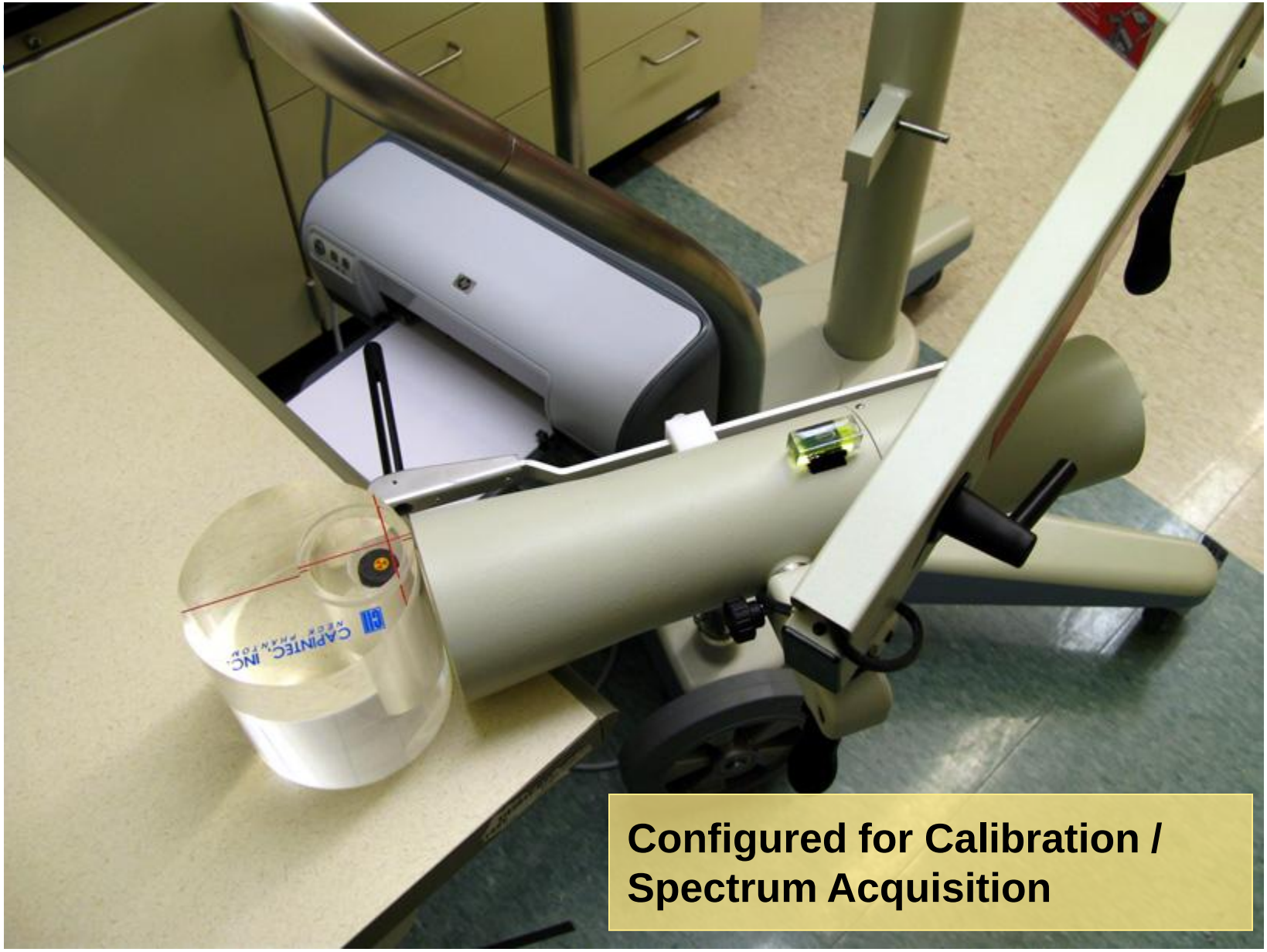
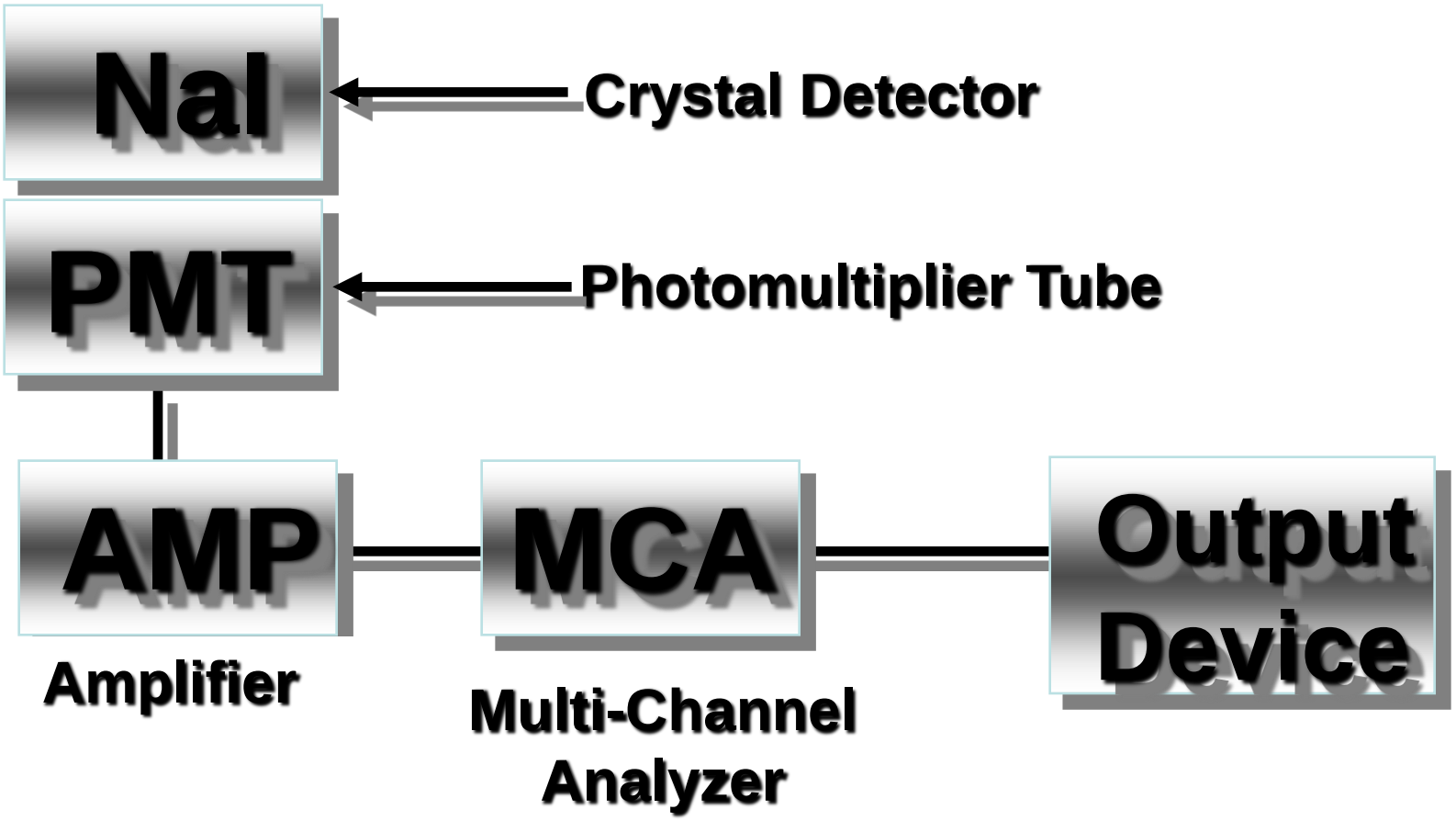


Configured for Calibration / Spectrum Acquisition

NaI Scintillation Detector



Radiation Detection
Scintillation Detectors

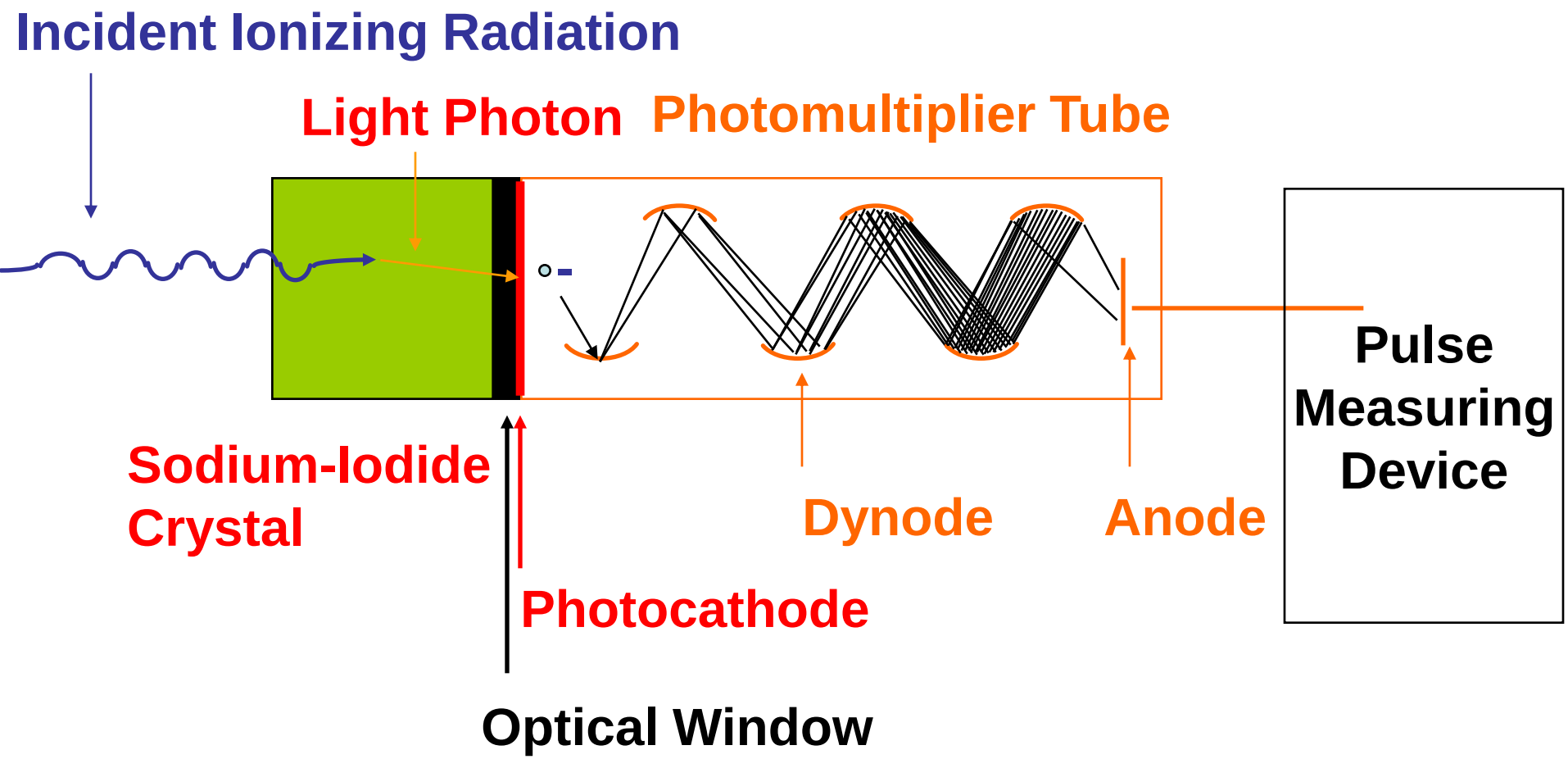


Diagram Credit:
HPS STW Technical Presentation

Liquid Scintillation Counters (LSC)

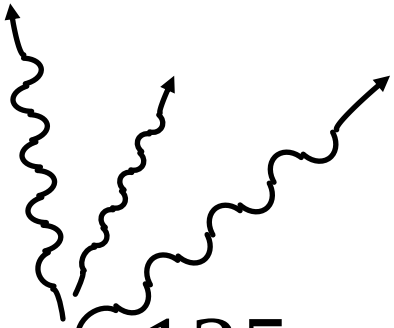
Gamma Counters

Picture Credits:
(Various used equipment on-line sales listings.)

Modern Gamma Counters

Picture Credit:
Product Brochure from PerkinElmer formerly Wallac

Iodine-125 Decays by Electron Capture



$$^{125}_{53}I + {}^{0}_{-1}electron \rightarrow {}^{125}_{52}Te + {}^{0}_{0}\nu\,(neutrino)$$

Results in Multiple, Discrete Photons Emitted

Primary Photons for I-125

Photon Mode	KeV	% Abundance
Te K alpha 2	27.2	40.5
Te K alpha 1	27.5	75.6
Te K beta 1	31.0	20.1
Te K beta 2	31.9	4.4
γ M1+0.07%E2	35.5	6.7

Reference:
Brown, E and Firestone, R.; Table of Radioactive Isotopes, 1986.

Primary Photons for I-129

Photon Mode	KeV	% Abundance
Xe K alpha 2	29.5	20.5
Xe K alpha 1	29.8	37.8
Xe K beta 1	33.6	10.2
Xe K beta 2	34.6	2.4
γ M1+ 0.08%E2	39.6	7.5

Reference:
Brown, E and Firestone, R.; Table of Radioactive Isotopes, 1986.

Ratio of Photons

Isotope		Photon Abundance (Per decay)
Iodine-129		0.785
Iodine-125		1.473

Equivalency or Conversion Factor:

- Going from I-129 activity to I-125 activity divide by 0.533.

Reference:

Brown, E and Firestone, R.; Table of Radioactive Isotopes, 1986.

Modern Gamma Counters

Picture Credit:
Product Brochure from PerkinElmer formerly Wallac

Absolute Efficiency?

- "Absolute detector efficiency—for I-125, it is possible to determine the absolute efficiency of the detector by using the Horrocks method. The method does not require calibrated sources (having a known DPM value). For other isotopes, detector efficiency is obtained by dividing corrected CPM in the counting window by the isotope DPM value. This method does require the use of calibrated sources."

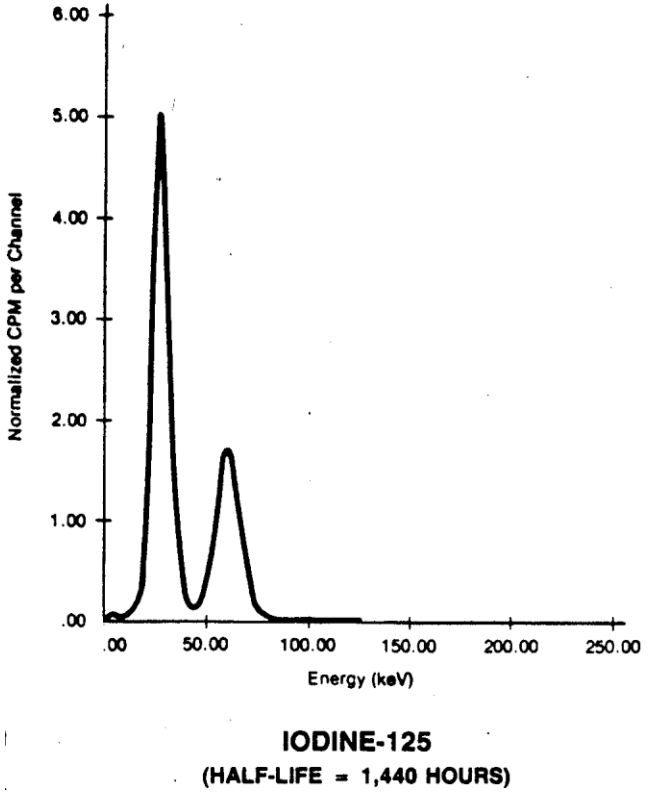
From Perkin-Elmer Website

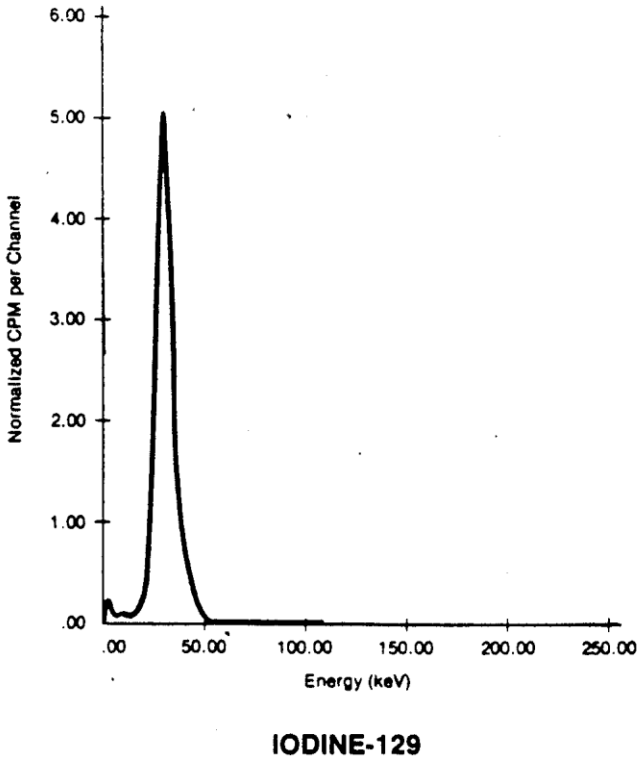
las.perkinelmer.com/Catalog/ProductInfoPage.htm?ProductID=2470-0010

References:

1. **Eldrige, *Nucleonics*, 22 (6), 56 (1964)**
2. **Harper et. al, *J. Nucl. Med.* 4, 277 (1963)**
3. **Horrocks, *Clinical Chemistry*, Vol. 21, No. 3, (1975)**

I-125 and I-129 Gamma Spectra





Reference: (Scanned page)
Packard AutoGamma 5000 Series Manual; Appd. B-13; 1989.

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Data/Observations

Iodine-129

- 0.23% Iodine-129 Efficiency

Iodine-125

- 0.43% Iodine-125 Efficiency
  - Minimum Detectable Activity of 0.06 μCi
- Fewer counts in the sum (coincident) peak than with bench top gamma counting instruments.

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Future Work

- Acquire Iodine-125 spectrum under conditions of significant dead time.
- Validate with NIST traceable standard of Iodine-125
- Cross calibrate NIST Traceable Iodine-125 with NIST Iodine-129 traceable standard.
- Check on the derivation of the Reg. Guide Organ Burden.

Reference Materials

1. Cember, Herman: An Introduction to Health Physics; 2nd edition, 1987.
2. U.S. Nuclear Regulatory Commission Regulatory Guide 8.20, "Applications of Bioassay for I-125 and I-131," September, 1979.
3. U.S. Nuclear Regulatory Commission Regulatory Guide 8.9, "Acceptable Concepts, Models, Equations and Assumptions for a Bioassay Program," Revision 1, July 1993.
4. Packard Model Autogamma 5000 Operating Procedures Manual, [Operating Procedures and Appendixes.

Reference Materials

5. PerkinElmer Model 1470 Wizard Gamma Counter Instrument Manual, [Operating Procedures and Appendixes.]
6. Brown, E. and Firestone, R.; Table of Radioactive Isotopes, 1986.
7. Capintec CAPTUS 3000 Portable THYROID UPTAKE SYSTEM, [Owner's Manual]; Rev. D – February 2010.

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Physics Before Chemistry

"Physics is the knife that cuts through the grain of nature."

Unattributed-Unknown

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