ANNEX 3 TO THE DRAFT REPORT OF THE OECD VALIDATION OF THE RAT HERSHBERGER BIOASSAY: PHASE 2

Hershberger Assay Interlaboratory Study: Statistical analysis of phase 2 data from 16 laboratories in the multi-chemical dose response study

Hershberger Assay Interlaboratory Study: Statistical analysis of Phase 2 data from 16 Laboratories in the Multichemical dose response study.

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Data were collected in sixteen labs from the UK, Europe, US, Japan and Korea as per prior plans for doses and chemicals (Table 1) and submitted to OECD and to the Lead laboratory in Microsoft Excell format for analysis. Upon receipt, Microsoft Excell files were converted using WordPerfect 9 software to text files, which were transmitted using ftp to the US Environmental Protection Agency IBM Model 9672 (Serial number 0116F0, V01R04M00 platform) and analyzed statistically using SAS (r) proprietary software release 8.2 (TS2M0) licensed to USEPA, Site 0045713001.

Means, standard errors, coefficients of variation (CVs) were calculated by SAS using PROC MEANS. For statistical analysis of the dose-response data log 10 transformed data were analyzed using PROC GLM with dose as a class variable. This analysis did not include positive and negative control data so the p-, F- and R2 values are representative of the strength of the dose response along and not the positive or negative control values. Data for all analyses were log 10 transformed for consistency in the analysis, being required due to heterogeneity of variance in many of the studies.

Body weight at necropsy was used as a covariate in the analysis of the data for the liver, kidney and adrenals, organs which covary with body weight. After inspection of the data analyses, ANCOVA with body weight was not included for the reproductive organs because they do not covary with body weight and the inclusion of this covariate did not impact on outcome of the data analyses.

Treated groups were compared to the control (castrate plus testosterone propionate-TP only for antiandrogens or castrate plus vehicle for androgens) using the LSMEANS option of PROC GLM. LSMEANS is a two-tailed t-test which allows for comparison of all groups to one another and is appropriate for these studies because their effects in the Hershberger assay had already been demonstrated by the Lead laboratory or in other

laboratories and we had a-priori hypothesis about the direction of the effects of these chemicals on each of the endpoints. In a few cases, where a laboratory failed to detect the expected endocrine activity, as determined by a significant F-value on the PROC GLM ANOVA, the data were reanalyzed by linear regression to see if there was a significant trend in the data.

The pooled GLM analysis also included the main effect of "laboratory" to see if the labs differed from one another and, more importantly, included the "laboratory by dose" interaction to determine if there were significant differences in the dose response of the androgenic tissues from lab to lab. The results of these analyses are included in the enclosed tables along with the dose effect by lab, with means and CVs by dose and lab. As certain factors such as exact age at necropsy, rat strain and body weight were not standardized across the labs in the current phase of the project, as they were unlikely to influence the outcome, we expected that the lab to lab variability would be statistically significant, although biologically unimportant. In most cases, the lab by dose interactions were not statistically significant or were relatively small as compared to large main effects.

The study was conducted using two protocols. In this document the first will be referred to as the EU or European protocol (nine laboratories) with second protocol being termed as the Japanese protocol (seven laboratories). Each individual laboratory studied 3-4 chemicals as per Table 1. In the EU protocol, antiandrogenic chemicals were administered orally with 0.4 mg TP/kd/d whereas the Japanese protocol used 0.2 mg/kg/d.

In Japan, 4-5 laboratories studied methytestosterone (MT-an androgen in), vinclozolin (V-an antiandrogen) and p,p' DDE (an antiandrogen). Nine laboratories studies using the EU protocol included these three chemicals and the androgen trenbolone (TREN-an anabolic steroid), and the antiandrogens procymidone (P), linuron (L) and finasteride (F).

While MT and TREN are both androgenic they were not expected to produce identical profiles of alterations due to significant differences in their chemical structures, ADME and metabolism. In addition, V, P, L and DDE antagonize growth of the androgen-dependent tissues by acting as androgen receptor (AR) antagonists whereas F inhibits the enzyme 5 alpha reductase (which normally converts testosterone (T) to a more active androgen dihydrotestosterone (DHT)) but F does not bind AR. Hence, we did not expect F to produce the same profile of effects as the AR antagonists due to the tissue specific roles of 5 alpha reductase and DHT in the male rat reproductive tract.

Data for the androgen-dependent tissues including the ventral prostate (VP), seminal

vesicle plus coagulating glands with fluid (SV), levator ani plus bulbocavernosus (LABC) muscles, Cowper's glands and glans penis (GP) were analyzed for dose effects by laboratory for each of the seven chemicals and then the data from 3-5 laboratories that executed the same study were pooled and the data were examined for the magnitude of the dose and laboratory effects and their interaction. The results of these analyses are presented in tables by study displaying the means, CVs, p- ,F- and R square (R2) values.

The R2 value indicates the strength or robustness of the dose and laboratory effects on a particular endpoint. In this exercise, R2 values are useful in comparing the how robust the dose effect is from laboratory to laboratory and how large the difference is between laboratories. R2 values also are used to compare the responsiveness of the different endpoints to one-another to determine which are more or less affected by the different treatments. We expected that different mechanisms of action would produce different profiles of effects such that one endpoint would not always be more sensitive to disruption than another.

As indicated above, MT, DDE and vinclozolin were studied using both EU and Japanese protocols. For V the two groups used the same doses while for the MT and DDE studies the doses used were not the same. The data for these two protocols were compared to one-another for three chemicals were compared to each other, given the limitations of the experimental designs. MT and DDE dose response data were compared for each endpoint visually and ED50s were generated from the data sets. As the results were obviously very similar in their ability to detect the effects of MT or DDE, no further analysis was conducted. For V, the data sets were pooled and examined for protocol by dose interactions for each endpoint. LSMEANS also was used to determine the LOEL for each protocol in the pooled analysis. We also examined the LOELs on a laboratory to laboratory basis to see if one protocol was distinctly more sensitive than the other. It was expected that the 0.4 mg TP/kg/d group would produce larger tissues that might be easier to necropsy than the 0.2 mg TP/kg/d group but we wanted to know if the higher dose of TP would reduce the sensitivity of the assay. However, a reduction in sensitivity of the assay was not anticipated because the TP dose-response study from Phase 1a of the OECD interlaboratory study indicated that the dose 0.4 mg TP/kg/d was on the linear portion of the dose-response curves and not at the Bmax for each of the five androgen-dependent endpoints.

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I.A Methyltestosterone (MT).

MT is methylated steroid that is very effective orally because the C-17 methyl group prevents first pass metabolism by the liver upon absorption from the gut. It is a well characterized androgen that is known to be effective in stimulating androgen-dependent tissue weights in the Hershberger assay. Via this route of administration, MT is much more potent than the natural hormones T and DHT. It also is more potent orally than TREN, the other synthetic androgen used in the current investigation.

Four labs administered MT from the EU group at dosage levels of 0, 0.5, 2, 10 and 40 mg/kg/d by gavage. Four labs from Japan administered MT at 0, 0.05, 0.5, 5 and 50 mg/kg/d. The high dosage levels of MT used by each group were expected to produce robust responses on all five androgen-dependent tissues. The R2 values for the EU group and Japan MT studies are shown in tables 1 and 2 respectively with the GP being least robustly affected. MT also affects the liver and other nonreproductive organ weights and physiology.

I.A.1 EU protocol results. MT versus castrate plus vehicle.

MT at 40 mg/kg/d significantly (p , 0.01) stimulated growth of all five androgen-dependent organs is each of the four labs (Tables 3-7 and Figures 1-10) with R2 values ranging from 52 (GP) to 82% (LABC). The SV, VP and Cows had R2 values similar to, but slightly lower than the LABC. Note that cells shaded yellow and blue differ significantly from control (castrate plus vehicle) at $p < 0.05$ or 0.01, respectively. On the Figures, a single asterisk denotes $p < 0.05$ while two asterisks denotes $p < 0.01$ pooled over all labs in the study. The Figures for the androgen-dependent tissues are generally displayed pooled over the labs first, followed by the data for the individual labs. The left panel of most figures displays bar graphs of the means and SE of the mean (not corrected for the lab to lab effect) while the right panel displays the same data so the shape of the dose-response can be visualized.

LOELS ranged from 2 to 40 mg/kg/d from lab to lab for each endpoint (Tables 3-7). Pooled over labs, the LOELS were 2, 10, 2, 10, and 2 mg for the VP, SV, LABC, GP and Cows, respectively.

MT treatment also altered growth of the adrenals, liver and kidneys (Table 8-10 and Figures 11-13, respectively). MT reduced adrenal size at 40 mg in each lab and increased liver weight at 40 mg in each lab and kidney weight at 10 and 40 mg in three of four labs. As indicated above, body weight at necropsy was included as a covariate in these analyses. It has a significant impact on the outcome, reducing the error means square of the ANOVA

used to calculate the p-value for the MT dose effect, especially for the liver. Body weight was not significantly affected by MT administration (figure 14).

I.A.2 Japan MT protocol results. MT versus castrate plus vehicle.

MT significantly stimulated the growth of all five androgen-dependent tissues at 50 mg in every lab and at 5 mg in most labs (Tables 11-15, Figures 15-22) . Pooled over the labs every tissues was significantly stimulated at 5 and 50 mg MT/kg/d while no effects were seen at 0.5 or lower. Liver, kidney and adrenal weights were only measured in two of the four labs but these data showed the same trends as the EU data, with MT reducing adrenal weight (Figure 23) and increasing liver and kidney weights (Figures 24 and 25, respectively). Body weight at necropsy was not affected by MT administration at any dose (Figure 26).

I.A.3 EU verus Japan MT protocol results.

Figure 27 displays the MT dose response data for the SV, VP, LABC and GP tissues from both groups. It is obvious, as expected, that both groups (four labs each for a total of eight labs) obtained almost identical results for each tissue with the shapes of the dose-response curves being linear over the dose range employed by each group.

I.B Trenbolone.

Trenbolone is an anabolic steroid used to promote growth in domestic animals, especially beef cattle, in some countries. It is a high affinity ligand for the AR and acts as an AR agonist in vitro and in vivo. Being a C-19 norandrogen, however, its physiological properties differ considerably from the natural hormone testosterone and, unlike MT, data from the Lead laboratory indicate that it is much less effective in the Hershberger assay when administered orally verus injection. Trenbolone is easily metabolized by the liver because it is not methylated in the C-17 position.

I.B.1 EU Results with Trenbolone

As seen in Table 1, the sensitivity of the androgen-dependent endpoints differs between trenbolone and MT. For trenbolone the R2 values are much lower for the VP, SV and Cows than they are for the LABC and GP tissues. The GP has the second ranked R2 for this androgen, whereas it had the lowest R2 value with MT treatment. This contrast is evident in Figure 28. As compared to MT, trenoblone has relatively lesser effect on tissues like the VP which display high levels of 5 alpha reductase activity than it does on the LABC which, in contrast to the VP, is much more dependent upon T for growth than DHT. Such a profile is common for a C-19 norandrogen and there are several publications

describing the biochemical basis for this in the literature. In general, the profile and dose response obtained here with oral trenbolone, is identical to what our laboratory has published.

Trenbolone significantly stimulated VP, SV, LABC, GP and Cows weights at 8, 40, 8, 40 and 8 mg, respectively (Tables 16-20, Figures 29-38). In contrast to MT, oral trenbolone did not affect adrenal, liver, or kidney weights (Figures 39, respectively) but did significantly reduced body weight (at 40 mg, Figure 40).

II. Antiandrogens: Androgen Receptor antagonists:

This phase of the Hershberger assay validation program included four environmental chemicals that act as androgen receptor antagonists. All of them have been examined in this assay previously and the high dose levels were selected to determine if known effects could be detect by all participating labs. Several lower dosage levels also were included in order to determine LOELs and NOELs for each chemical. Each of the four chemicals has been shown to be an AR antagonist in vitro in at least two laboratories and each displays developmental effects consistent with this endocrine activity (in our laboratory and in at least one other lab). However, the potency in utero and the profile of effects seen in the reproductive tract of the male offspring is not identical. In the Hershberger assay the Lead lab has shown that V and P are effective in this assay at doses of 25 mg/kg and above and p,p' DDE and linuron are effective at 100 mg/kg. The effects of V, P, L and DDE all have replicated by other labs using the Hershberger assay.

II.A Antiandrogens: Androgen Receptor antagonists: Vinclozolin

Vinclozolin, a dicarboximide fungicide, is a well characterized AR antagonist in vitro and in vivo. This chemical was studied at the same dosage levels at 0, 3, 10, 30 and 100 mg/kg/d by both groups. In the EU protocol, V was competed against 0.4 mg TP whereas the Japanese groups used 0.2 mg TP. Of the three chemicals studied in common, this is the only chemical a direct statistical comparison is possible because the same dosage levels were used by both groups.

II.A.1 EU protocol. Vinclozolin versus 0.4 mg TP/kg/d – four labs

Across the four labs vinclozolin significantly reduced VP, SV, LABC, GP and Cows weights (Table 21-25, Figures 41-50, respectively). Being significant at 30 mg V for all endpoints except the GP which was significantly affected at 100 mg/kg/d. In terms of the robustness of the responses, the SV, LABC and VP were all more affected (R2 = 81, 76, and 71%, respectively) than the Cows (R2=63%) or the GP (R2=43%) (Table 1). This pattern was generally the case for all the AR antagonists.

On a lab to lab basis, every lab detected a reduction in at least one of the androgen-dependent tissues at 30 mg/kg/d. In fact, every tissue except the GP was significantly affected in every lab. The GP was affected in three of four of the labs. In this study, lab #7 displayed an usually large CV for the Cows (80%), likely due to an errant entry for one of the six animals. This inflated the overall CV in the ANOVA model for this lab, and reduced the F and R2 values, as compared to the other labs, but this still did not impact on the ability to detect and effect of V at 100 mg ($p < 0.01$).

As noted by the Lead laboratory in their studies of V, V-treatment also significantly increased adrenal and liver organ weights at 30 and 100 mg/kg/d (Tables 26 and 27, Figures 51 and 52) without significantly affecting body weight at necropsy (Figure 53). These effects also were significant in each of the four labs individually.

II.A.2 Japan protocol. Vinclozolin versus 0.2 mg TP/kg/d – four labs

Pooled over the four labs vinclozolin significantly reduced VP, SV, LABC, GP and Cows weights (Table 28-32, Figures 54-63, respectively). Being significant at 10 mg V and above for all. In terms of the robustness of the responses, the SV was more affected (R2=91%) than the LABC, VP, Cows or GP (R2 = 82.8, 81.3, 78 and 74.2%, respectively) (Table 2).

On a lab to lab basis, every lab detected a reduction in at least one of the androgen-dependent tissues at 10 mg/kg/d and only 4/20 effects were not significant at 30 mg/kg/d. At 100 mg/kg/d all endpoints were affected at 100 mg/kg/d, $p < 0.01$.

Although adrenal and liver weights were measured only in one of the four labs they did appear elevated(Figures 64 and 65).

II.A.3 EU versus Japan compared for Vinclozolin

The data from the two groups for vinclozolin were pooled and analyzed to determine if they were significant differences between the protocols. We expected a significant main effect of protocol with higher values for androgen-dependent tissues for the EU protocol because the EU group used twice as much TP sc as did the Japan group. What we wanted to know was if the dose response curves were parallel or not (as indicated by a dose by protocol interaction), or if one protocol consistently achieved lower LOELs on a lab to lab basis than did the other. We felt that the larger tissues in the 0.4 mg TP protocol would be easier to weigh but the 0.2 mg TP group could be slightly more sensitive. These questions

were also posed for the p,p' DDE data, a chemical which was run in both protocols. In this regard, we wanted to know if one protocol appeared better than the other (more sensitive to low doses of an antiandrogen), was this consistent across chemicals or was this sensitivity only apparent with a single chemical. Previously in Phase 1b, we had run both doses of TP (0.2 and 0.4 mg/kg/d) in a flutamide dose response study and in that study the 0.2 TP protocol did not display any advantage over the 0.4 mg TP protocol.

The results of the pooled ANOVA are displayed in Figure 66. Many of the pooled dose response curves failed to display an obvious threshold, being linear in the low dose region.

Administration of 0.4 mg TP as compared to 0.2 mg did increase tissue weights in four of five cases with the higher dose producing larger VP, SV, Cow and GP weights whereas the LABC weights were similar. The lack of effect of 0.4 mg TP versus 0.2 mg TP for the LABC was not anticipated because in Phase 1a of the OECD Hershberger assay validation program administration of 0.4 mg TP increased LABC weights to 70% of maximum verus 50% at 0.2 mg TP (data from 16 laboratories with each lab running a TP dose response). It is therefore proposed that the lack of difference in LABC weights in the current phase is likely due to the fact that we are comparing results among different labs rather than within labs. It is noteworthy, in this regard, that the rats in the Japan protocol were heavier (322 g) than those used for the EU study (285 g) with one of the EU rat strains being quite small (222 g) and having smaller LABCs at necropsy (267 mg versus 307 mg in the other three labs.

There is some indication when the data were pooled over the four labs that the Japan protocol was more sensitive to vinclozolin. For each organ, significant effects were seen at 10 mg V against 0.2 mg TP as opposed to 30 mg V against 0.4 mg TP. However, the V dose by TP dose interaction did not approach significance for most of the endpoints, indicating that the dose response curves are not different consistently. Furthermore, when the LOELs are examined on a lab by lab basis, the manner in which the protocol would be run and interpreted once implemented, there is no clear difference between the protocols. As shown in Figure 67, the LOELS vary for each endpoint from lab to lab, but one protocol does not show consistently lower LOELs than the other. It was also noted that the CVs for the labs in the Japan V study were slightly smaller than the CVs for the labs in the EU study which would affect the statistical analysis but is unlikely to be a function of the protocols, but rather, result from the inherent precision within each of the labs. While the interpretation of these results are arguable, the picture is clearer in comparison between the protocols for the p,p' DDE data that follow later in the report. For p,p' DDE, it is clear that the 0.2 mg TP protocol does not offer greater sensitivity to p,p' DDE, similar to the results of the flutamide Phase 1 study.

II.B Antiandrogens: Androgen Receptor antagonists: Procymidone

Procymidone, like V is a dicarboximide fungicide that displays AR antagonistic properties in vitro and in vivo. It generally has a potency in vivo equivalent to V. We have found that P effectively antagonizes TP in the Hershberger assay at dose of 25 mg/kg/d and above. Effects are seen on adrenal and liver weights at slightly higher dosage levels in this assay.

II.B.1 EU protocol results with procymidone

P was coadministered with 0.4 mg TP/kg/d at 0, 3, 10, 30 and 100 mg/kg/d. The rank order of the R2 values, indicative of the strength of the P dose reponse was similar to V with the GP showing the least robust response (Table 1). (R2 = 37% versus SV=78, VP=76, LABC=67 and Cow=63%). The means and CVs are shown in Tables 33-37 and the Figures are 68-77 for the VP, SV, LABC, GP and Cows respectively.

Pooled over the four labs, the VP, SV, LABC and Cow were significantly reduced ($p < 0.01$) at 10 mg P/kg/d. The GP was significantly reduced at 30 mg P. As with V, many of the pooled dose response curves failed to display an obvious threshold, being linear in the low dose region.

On a lab by lab basis, each lab detected the antiandrogenic effects of all of the tissues, except the GP which was not affected in 2/4 labs by P treatment. Three of 4 labs found some antiandrogenic effect at 10 mg P while the fourth lab LOEL of 30 mg P. As with V, many of the pooled many of the pooled dose response curves failed to display an obvious threshold, being linear in the low dose region.

Procymidone increase adrenal and liver weights at 30 and 100 mg/kd/d (Tables 38 and 39, Figures 78, 79) when the data were pooled over the labs but on a lab to lab basis 2/4 labs did not detect the adrenal effect. P also induced a dose related reduction in body weight at necropsy (Figure 80) being significant at 10 mg/kg/d in the pooled data set.

II.C Antiandrogens: AR antagonist p,p' DDE

We reported in 1995 that p,p' DDE and other DDT metabolites were AR antagonists with sufficient potency to alter pubertal maturation, induce malformations in male rat offspring exposed in utero and produce alterations in androgen-dependent tissues in the Hershberger

assay. All of these in vitro and in vivo observations have since been replicated in other laboratories. At 100 mg p,p' DDE/kg/d all androgen-dependent tissues were reduced in size as compared to the TP control in our study and in other Hershberger assay studies. Furthermore, DDE has potent effects on the liver and adrenal, with effects on the liver often occurring at dosage levels below those that affect androgen-dependent tissues.

The effects of p,p' DDE in this assay was studied in the EU protocol using DDE doses of 0, 5, 16, 50 and 160 mg/kg/d whereas the Japan protocol administered DDE at 0, 3, 10, 30 and 100 mg/kg/d.

II.C.1 EU protocol. P,p' DDE versus 0.4 mg TP/kg/d – four labs

In the EU protocol when four labs administered p,p' DDE at the described dosage levels VP, SV, LABC, GP and Cow weights were reduced in every lab (Tables 40-44 ,Figures 81-90). The rank order of responsiveness to DDE by the various endpoints was similar to the other AR antagonists with R2 for LABC=81%, SV=73%, VP=71%, Cows= 70% and GP=56%.

Pooled over four labs the LOELs for the VP=50, SV=50, LABC=16, GP=50 and Cow=16. On a lab by lab basis, no effects were seen on any endpoint at 16 mg/kg/d but all four of the labs individually found effects at 50 and 160 mg.

DDE treatment did stimulate adrenal and liver weights (Table 45, 46 and Figures 91 and 92). The effect on the liver was significant at 5 mg, the only effect noted at this dose, and individually all four labs detected significant increases in liver weight at 16 mg/kg/d. The dose response data for the pooled results are often appear linear in the low dose range, especially for the effect on the liver. The effect on the adrenals was only seen in the 160 mg dose group in the pooled data set and was only detected in one of four labs at this dose when the data were analyzed on a lab to lab basis. Body weight was reduced overall the labs at 160 mg/kg/d (Figure 93).

II.C.2 Japan protocol. P,p' DDE versus 0.2 mg TP/kg/d – five labs

In the Japanese protocol when five labs administered p,p' DDE at the described dosage levels VP, SV, LABC, GP and Cow weights were reduced in every lab (Tables 47-51 ,Figures 94-103). The rank order of responsiveness to DDE by the various endpoints based upon the R2 value was SV= 76%, LABC=69%, VP=63%, Cows= 56% and GP=54%.

Pooled over five labs the LOELs for the VP=30, SV=30, LABC=30, GP=100 and Cow=30. On a lab by lab basis, no effects were seen on any endpoint at 10 mg/kg/d but 4/5 of the labs individually found effects at 30 while one lab only found effects at 100 mg.

DDE treatment did stimulate adrenal and liver weights but data were collected only in one of five of the labs (Figures 104 and 105). Body weight was not significantly reduced overall the labs at 100 mg/kg/d (Figure 106).

II.C.3 EU protocol versus the Japan protocol for p,p' DDE

As the two groups did not use the same dosage levels of DDE a direct statistical comparison, like the one made with V, was not possible. However, as both protocols included DDE dose levels that ranged from mildly to extremely effective in reducing the weights of the androgenic tissues it was possible to compare the shapes of the dose response curves visually and by calculating ED50s for the response to DDE administration.

Figure 107 displays the dose response data, based upon percent of the TP control, for normalized organ weights fro four of the tissues. For two tissues, the LABC and the Cows, the the DDE appeared to slightly more pronounced reductions in weight in the EU protocol using 0.4 mg TP than in the Japan protocol using 0.2 mg TP/kg/d. On the other hand, the reverse was true for the VP and SV tissues. When combined into a single variable, these four androgen-dependent tissues yielded dose response curves for the two protocols (0.4 versus 0.2 mg TP/kg/d) that were nearly identical (Figure 108). The log 10 ED50s, calculated using Sigma plot software, were 2.013 ±.49 mg DDE for the Japanese protocol versus 2.071 ±.019 for the EU protocol. These data indicate that for DDE using the lower dose of 0.2 mg TP/kg/d does not enhance the sensitivity of the Hershberger assay as compared to 0.4 mg TP/kg/d. The percent reductions in androgen-dependent organ weights were similar regardless of whether the animals were treated with 0.2 mg TP/kg/d or 0.4 mg TP/kg/d.

II.D Antiandrogens: Androgen Receptor antagonists: Linuron

Linuron is a urea-based herbicide that displays multiple endocrine and neuroendocrine toxicities. It is an AR antagonist, appears to inhibit fetal testis testosterone synthesis, has antithyroidal activity (lowering serum T4), alters CNS neuroendocrine activity and, at the higher end of the dose-response curve, displays acute anticholinesterase activity in vivo (SLUD at 200 mg/kg/d). When administered in utero, recent studies from two labs have shown that linuron induces malformations in androgen-dependent tissues in the male rat

reproductive tract. It also has been shown by the Lead lab that linuron reduces weights of the androgen-dependent tissues in the Hershberger assay at 100 mg/kg/d without inducing overt toxicity (SLUD) in immature-castrate animals dosed for 7 days but not in adult male rats dosed for 5 days. As demonstrated by the R2 values in Table 1, linuron produces less robust effects in the Hershberger assay (R2=45.6%) than does V, P, DDE or F (R2 about 65% for all four). Taken together, these results indicate that linuron is an excellent chemical for the interlaboratory study because overt toxicity is evident at dosage levels only two-fold above those are antiandrogenic. The AR antagonist activity should be detected in the Hershberger assay and it should be detected at or below the proposed MTD (10% reduction in body weight at necropsy or any overt toxicity).

II.D.1 EU protocol. Linuron versus 0.4 mg TP/kg/d – four labs

In the EU protocol when four labs administered linuron at 0, 3, 10, 30 or 100 mg/kg/d, the effects were not as robust as seen with V, P, DDE or F. VP, SV, LABC, GP and Cow weights not were reduced in every lab (Tables 52-56 ,Figures 109-118). The rank order of responsiveness to L by the various endpoints was similar to the other AR antagonists with R2 for SV=65%, LABC=63%, VP=59%, Cows=43% and GP=26%, but the values were lower because the effects were less robust.

Pooled over four labs the LOELs for the VP=100, SV=30, LABC=30, GP=100 and Cow=100 mg L/kg/d. On a lab by lab basis, no effects were seen on any endpoint at 10 mg/kg/d and three of four labs individually found effects at 30 and 100 mg. However at 30 and 100 mg L/kg/d only 4 of 20 and 14 of 20 possible responses were statistically significant. In one lab (lab #6), only SV weights were significantly reduced ($F=4.2$, $p < 0.05$ for by LSMEANS (two-tailed t-test) of 100 mg/kg/d). When the results from lab #6 were examined using linear regression to determine if there were significant trends in the data, both SV and LABC weights declined significantly with increase dose of L. While the VP is generally affected by AR antagonists to the same degree as are the SV and LABC weights, VP TP-control data appeared unusually variable (CV= 41%) and mean VP weight was only 83 mg. In the F study, lab #6 TP controls were less variable (CV=24%) and mean VP weight was 177 mg. In the other three labs, L reduced androgen-dependent tissue weights significantly at 100 mg/kg/d in 5/5, 4/5 and 4/5 cases. In summary, all four labs detected the antiandrogenic activity of L.

L treatment did not significantly affect adrenal and liver weights but body weight was reduced overall the labs at 100 mg/kg/d (Figure 119) by about 25 g or about 7% (F (4, 117 df) = 8.5 for dose, $p < 0.01$ at 100 mg/kg/d). On a lab to lab basis, L signficantly reduced body weight at necropsy in one of the four labs.

III. Antiandrogen: DHT synthesis inhibitor. Finasteride

Finasteride is an orally active pharmaceutical azasteroidal antiandrogen that competitively inhibits 5 alpha reductase preventing the conversion of testosterone to dihydrotestosterone. F selectively blocks androgen action in tissues such as the prostate where continuous production of DHT is essential but has less effect in the LABC where T is the primary androgenic hormone. F-treatment reduces DHT tissue levels without affecting the AR or androgen action. Tissue T levels do not decline following F treatment, and, in fact, T levels may even increase in tissues in which 5 alpha reductase is inhibited. Of the antiandrogen used in the current phase, F clearly was more potent than the antiandrogenic pesticides V, P, L and DDE.

1. EU Protocol. Finasteride versus 0.4 mg TP/kg/d – four labs

In the EU protocol, F was administered orally at 0, 0.2, 1, 5 and 25 mg/kg/d in four labs. Marked weight reductions were seen in all the VP, SV, LABC, GP and Cow at all dosage levels, including 0.2 mg F/kg/d (Tables 57-61, Figures 120-129). As expected based upon the mechanism of action, the rank order of responsiveness of these tissues to F was very different from the AR antagonists (Table 1) with the LABC being relatively less affected by F than were the VP, SV or Cows. R2 for LABC=56%, SV=82%, VP=71%, Cows=64% and GP=44%.

Pooled over four labs the LOELs for the VP, SV, LABC, GP and Cow all = 0.2 mg F/kg/d. On a lab by lab basis, only one lab (lab #2) failed to detect any antiandrogenic effect at 0.2 mg F/kg/d which may have resulted from the relatively high average CV for the five endpoints (26.6%) for the F study in this lab versus the three other labs in this study (average CVs= 18.6, 19.8, 13.4) (Table 62).

F treatment significantly ($F(4, 118\ df)=3.1$ $p< 0.02$) reduced adrenal weights at 1, 5 and 25 mg F/kg/d (Figure 130) but it did not significantly affect liver or body (Figure 131) weights although liver weight was increased from 13.6 ± 0.5 g in the TP control group to 14.3±0.6 g at 25 mg F ($F(4, 118\ df)=1.9$, $p > 0.25$).

The dose response relationships between finasteride-treatment and the androgen-dependent tissues does not display traditional dose-response profiles. Typically, as one increases the dose of an antiandrogenic chemical there is a decrease in the organ weight until the weight approaches the value of a castrate-no TP animal. Such dose-response curves were seen in Phase 1b of the Hershberger assay validation program with the potent AR antagonist

flutamide. However, with finasteride the dose response curves (based upon percent of TP control) do not show the typical responses, especially at the higher dosage levels (Figure 132). At low dose levels, finasteride is more effective on a mg/kg/d basis than is flutamide in inhibiting the action of androgens on the VP, SV and GP (Fig 132). However, as the dose of finasteride is increased from 1 to 25 mg/kg/d the responses are not increased with dose, in contrast to he effects of increasing dosage levels of flutamide. The differences between the finasteride "plateaus" and the flutamide effects at 10 mg/kg/d on the different tissues provide a clue to the relative importance of 5 alpha reductase and DHT in each tissue. It is evident that the VP and SV are more affected by finasteride at high dosage levels than are the LABC or the GP, indicating that his enzyme and DHT are more important in the VP and SV than the LABC or GP. However, even for the VP and SV the curves for finasteride "plateau" at a level of inhibition above that obtained with flutamide. This occurs because inhibition of DHT formation in the VP and SV by finasteride does not prevent T from binding AR and stimulating tissue growth, even if it is not the "natural" androgen in these tissues. In summary, the LABC and GP are relatively less affected by finasteride than are the VP and SV. This contrasts nicely with the effects of trenbolone, which may be inactivated in tissues with 5 alpha reductase, such that the LABC and GP are more affected than the VP or SV. These contrasting results are important because they indicate the value of different androgen-dependent tissues in detecting agonists and antagonists with different mechanisms of action.

Endpoints, Lab to lab variability and recommendations.

Chemical Substance Assignment for Hershberger Phase 2
Positives - Laboratory Distribution – for Dose Response

Laboratory		Methyltest.	Trenbolone	Vinclozolin	Procymidone	Linuron	*p,p'*-DDE	Finasteride
LAB # 9	**3**				**X**		**X**	**X**
2	**3**	**X**			**X**			**X**
6	**3**	**X**				**X**		**X**
3	**3**		**X**	**X**			**X**	
1	**3**		**X**	**X**		**X**		
4	**3**	**X**				**X**	**X**	
7	**3**		**X**	**X**	**X**			
5	**3**			**X**		**X**		**X**
8	**3**	**X**			**X**		**X**	
Japan								
10	**2**			**X**			**X**	
11	**3**	**X**		**X**			**X**	
12	**1**						**X**	
13	**2**	**X**		**X**				
14	**2**			**X**			**X**	
15	**1**	**X**						
16	**2**	**X**					**X**	

Table 2

R2 — ANTIANDROGENS - EUUKAS

DDE	VP	SV	LABC	GP	COWS	*AVERAGE*	RANK
Lab 3	79	85	89	67	82	**80.4**	1
4	47	39	83	31	61	**52.2**	4
8	86	89	74	62	66	**75.4**	2
9	60	79	78	65	72	**70.8**	3
AVERAGE	**68**	**73**	**81**	**56**	**70**	**69.6**	
RANK	**4**	**2**	**1**	**5**	**3**		

VIN	VP	SV	LABC	GP	COWS	*AVERAGE*	RANK
Lab 1	84	85	84	75	72	**80**	2
3	63	72	65	44	69	**62.6**	4
5	62	86	75	14	61	**90.6**	1
7	74	80	80	38	49	**64.2**	3
AVERAGE	**71**	**81**	**76**	**43**	**63**	**66.8**	
RANK	**3**	**1**	**2**	**5**	**4**		

PROC	VP	SV	LABC	GP	COWS	*AVERAGE*	RANK
Lab 2	74	59	57	23	50	**52.6**	3
7	62	77	40	34	44	**51.4**	4
8	88	84	88	57	68	**70.8**	2
9	78	90	83	34	90	**75**	1
AVERAGE	**75.5**	**77.5**	**67**	**37**	**63**	**62.5**	
RANK	**2**	**1**	**3**	**5**	**4**		

FINASTERIDE	VP	SV	LABC	GP	COWS	*AVERAGE*	RANK
Lab 2	70	70	37	13	44	**46.8**	4
5	69	93	72	69	88	**78.2**	1
6	64	75	47	42	49	**55.4**	3
9	82	90	67	50	76	**73**	2
AVERAGE	**71**	**82**	**56**	**44**	**64**	**63.4**	
RANK	**3**	**1**	**2**	**5**	**4**		

LINURON	VP	SV	LABC	GP	COWS	*AVERAGE*	RANK
Lab 1	67	80	73	41	67	**65.6**	2
4	67	61	67	20	38	**50.6**	3
5	74	77	86	29	64	**66**	1
6	26	41	27	12	2.5	**21.7**	4
AVERAGE	**58.5**	**65**	**63**	**25.5**	**43**	**45.6**	
RANK	**3**	**1**	**2**	**5**	**4**		

OVERALL	VP	SV	LABC	GP	COWS
R2	**68.8**	**75.7**	**68.6**	**41.1**	**60.6**
RANK	**2**	**1**	**3**	**5**	**4**

Table 2 continued

R2	ANDROGENS						
MT	**VP**	**SV**	**LABC**	**GP**	**COWS**	***AVERAGE***	**RANK**
Lab 2	68	64	84	57	69	**68.4**	3
4	83	86	76	55	80	**76**	2
6	67	66	80	37	73	**64.6**	4
8	91	85	89	59	87	**82.2**	1
AVERAGE	**77**	**75**	**82**	**52**	**77**	**72.6**	
RANK	**2**	**4**	**1**	**5**	**2**		

TREN	**VP**	**SV**	**LABC**	**GP**	**COWS**	***AVERAGE***	**RANK**
Lab 7	53	51	69	61	39	**54.6**	1
3	18	57	77	60	58	**54**	1
1	64	31	68	65	42	**54**	1
AVERAGE	**45**	**46**	**71**	**62**	**46**	**54.2**	
RANK	**5**	**3**	**1**	**2**	**3**		

Table 3 Ventral Prostate EU | Methyl Testosterone (oral gavage) mg/kg/d ten days

DOSE OF MT (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	0.5	2	10	40	Necropsy BODY WT	OVERALL	F VALUE MT	R-SQUARE MT
Lab 2	MEAN	15.6	17.5	21.6	50.3	110	304	43	14	68%
TP=0.4	CV	36	45	53	50	32		47		
4	MEAN	24.7	26.8	50.5	75.5	163	327	68	31	83%
TP=0.4	CV	44	22	57	12	36		44		
6	MEAN	4.9	4.2	8.1	21.1	70	295	21.6	13	67%
TP=0.4	CV	66	37	59	102	37		71		
8	MEAN	18.8	21.1	24.8	62.5	151	320	56.8	62	91.00%
TP=0.4	CV	36	11	28	23	25		34		
ALL LABS	MEAN	16	14.2	26.2	52.3	123				77.00%
TP=0.4	CV	62	58	83	51	43				

ANOVA For VP			p VALUE	R2
Chemical effect	F=	68	0.0001	50.20%
Lab Effect	F=	53	0.0001	29.40%
Chemical*Lab	F=	0.9	0.52	

Data analyzed by SAS using Proc GLM with Log10 transformed data

Table 4 Seminal Vesicle EU | Methyl Testosterone (oral gavage) mg/kg/d ten days

DOSE (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	0.5	2	10	40	Necropsy BODY WT	OVERALL	F VALUE MT	R-SQUARE MT
Lab 2	MEAN	53.4	55.3	45	78.3	142	304	75	11	64%
TP=0.4	CV	55	29	39	49	19		36		
4	MEAN	54	64	77.6	111	247	327	111	39	86%
TP=0.4	CV	20	24	20	25	28		31		
6	MEAN	42	43	46	84	191	295	81.2	12	66%
TP=0.4	CV	51	32	30	57	21		38		
8	MEAN	58	62	64	117	305	320	123	34	85.00%
TP=0.4	CV	35	15	22	22	36		43		
ALL LABS	MEAN	52	56	58	98	221				75.00%
TP=0.4	CV	40	28	34	39	41				

ANOVA For SV			p VALUE	R2
Chemical effect	F=	73	0.0001	66.50%
Lab Effect	F=	12.5	0.0001	8.60%
Chemical*Lab	F=	0.8	0.65	

Data analyzed by SAS using Proc GLM with Log10 transformed data

Table 5 LABC EU

Methyl Testosterone (oral gavage) mg/kg/d ten days

DOSE (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	0.5	2	10	40	Necropsy BODY WT	OVERALL	F VALUE MT	R-SQUARE MT
Lab 2	MEAN	124	113	119	159	263	304	155	32	84%
TP=0.4	CV	22	12	19	11	9		14		
4	MEAN	213	214	306	327	496	327	311	20	76%
TP=0.4	CV	16	12	23	22	16		20		
6	MEAN	145	166	188	254	446	295	240	24	80%
TP=0.4	CV	26	23	7	29	9		19		
8	MEAN	188	215	230	349	524	320	304	49	89.00%
TP=0.4	CV	16	16	17	17	8		14		
ALL LABS	MEAN	168	175	211	272	432				82.00%
TP=0.4	CV	28	29	38	35	26				

ANOVA For LABC			p VALUE	R2
Chemical effect	F=	110	0.0001	52.80%
Lab Effect	F=	91.3	0.0001	33.00%
Chemical*Lab	F=	1.6	0.1	

Data analyzed by SAS using Proc GLM with Log10 transformed data

Table 6 Glans Penis EU | Methyl Testosterone (oral gavage) mg/kg/d ten days

DOSE OF MT (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	0.5	2	10	40	Necropsy BODY WT	OVERALL	F VALUE MT	R-SQUARE MT
Lab 2	MEAN	52.3	55.2	44.9	68.1	79.2	304	60	8.1	57%
TP=0.4	CV	13	13	28	24	14		19		
4	MEAN	50.4	56.9	65.1	66.6	78.9	327	63.6	7.6	55%
TP=0.4	CV	13	14	15	17	14		15		
6	MEAN	60.4	56.8	67.2	73.5	88.4	295	69	3.7	37%
TP=0.4	CV	17	22	16	28	18		21		
8	MEAN	50.5	56.3	52.7	67.8	90.3	320	64	8.7	59.00%
TP=0.4	CV	18	22	23	18	12		18		
ALL LABS	MEAN	53.4	56.3	57.5	69	84.2				52.00%
TP=0.4	CV	17	17	25	21	15				

ANOVA For SV			p VALUE	R2
Chemical effect	F=	23	0.0001	42.50%
Lab Effect	F=	3	0.04	4.30%
Chemical*Lab	F=	1.4	0.18	

Data analyzed by SAS using Proc GLM with Log10 transformed data

Table 7 Cowper's glands EU | Methyl Testosterone (oral gavage) mg/kg/d ten days

DOSE (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	0.5	2	10	40	Necropsy BODY WT	OVERALL	F VALUE MT	R-SQUARE MT
Lab 2	MEAN	5.9	4.2	6.4	9.9	19	304	9.1	14	69%
TP=0.4	CV	29	25	31	48	19		33		
4	MEAN	6.1	7.2	10.45	13.2	23.3	327	12	25	80%
TP=0.4	CV	31	15	34	22	26		29		
6	MEAN	0.7	1.9	2.3	6.9	17.4		5.8	17	73%
TP=0.4	CV	44	92	36	84	26	295	58		
8	MEAN	6.7	7.8	11.8	16.9	29.9	320	14.9	42	87.00%
TP=0.4	CV	25	32	22	11	15		19		
ALL LABS	MEAN	4.8	5.2	7.7	11.7	22.4				77.00%
TP=0.4	CV	59	55	57	46	30				

ANOVA For COWs			p VALUE	R2
Chemical effect	F=	61	0.0001	41.30%
Lab Effect	F=	66	0.0001	33.90%
Chemical*Lab	F=	4.1	0.0001	

Data analyzed by SAS using Proc GLM with Log10 transformed data

Table 8 adrenal glands EU

Methyl Testosterone (oral gavage) mg/kg/d ten days

Type III SS

DOSE (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	0.5	2	10	40		OVERALL	F VALUE MT
Lab 2	MEAN	65.9	61.3	51.4	62.1	53.5		58.9	3.22
TP=0.4	CV	18	16	15	12	13		14	
4	MEAN	56.8	56.2	58.8	51.7	46.7		51	2.86
TP=0.4	CV	10	13	10	13	14		12	
6	MEAN	55.6	54	59.9	53.8	46.3		53.9	2.6
TP=0.4	CV	4	16	21	5	10		13	
8	MEAN	50.6	51.5	49.5	53	47.2		50.3	0.4
TP=0.4	CV	9	10	20	22	14		16	
ALL LABS	MEAN	57.2	56	54.9	55.1	48.5			
TP=0.4	CV	15	15	18	15	14			

ANOVA For adrenals			p VALUE	
Chemical effect	F=	5.1	0.0009	
Lab Effect	F=	9.8	0.0001	
Chemical*Lab	F=	1.2	ns	
Body weight		F=	12	0.0008

Data analyzed by SAS using Proc GLM with untransformed data with body weight as a covariate

Table 9	Liver	EU	Methyl Testosterone (oral gavage) mg/kg/d ten days							Type III SS
DOSE (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS			0	0.5	2	10	40		OVERALL	F VALUE MT
Lab 2	MEAN		11.6	11.9	11.7	11.8	13.1		12	2.8
TP=0.4	CV		8	9	8	6	8		5.6	
4	MEAN		13.7	14.4	15.1	14.3	14.9		14.5	1.6
TP=0.4	CV		6	9	8	6	4		6	
6	MEAN		13.5	14.7	14.7	14.5	14.5		14.4	0.8
TP=0.4	CV		8	12	15	13	10		8	
8	MEAN		12.9	13.2	12.6	13.7	14.1		13.3	2.6
TP=0.4	CV		8	8	8	3	14		5	
ALL LABS	MEAN		13	13.6	13.5	13.6	14.2			
TP=0.4	CV		10	13	14	11	9			

ANOVA For Liver			p VALUE	
Chemical effect	F=	5.1	0.0009	
Lab Effect	F=	47	0.0001	
Chemical*Lab	F=	1.2	ns	
				0.000
Body weight		F=	68	1

Data analyzed by SAS using Proc GLM with untransformed data with body weight as a covariate

Table 10 Kidneys EU Methyl Testosterone (oral gavage) mg/kg/d ten days

DOSE (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	0.5	2	10	40		OVERALL	F VALUE MT
Lab 2	MEAN	2063	2127	2071	2127	2194		2116	0.26
TP=0.4	CV	10	8	9	4	8		6.8	
4	MEAN	2101	2214	2319	2318	2385		2268	2.7
TP=0.4	CV	4	12	9	7	7		7	
6	MEAN	2326	2434	2462	2542	2566		2466	2.6
TP=0.4	CV	9	7	13	9	11		7	
8	MEAN	2082	2190	2103	2405	2381		2233	5.1
TP=0.4	CV	6	8	7	8	4		7	
ALL LABS	MEAN	2143	2244	2239	2348	2381			
TP=0.4	CV	9	10	12	10	10			

ANOVA For Kidneys			p VALUE
Chemical effect	F=	7.6	0.0001
Lab Effect	F=	34	0.0001
Chemical*Lab	F=	0.6	ns
Body weight	F=	40.9	0.0001

Data analyzed by SAS using Proc GLM with untransformed data with body weight as a covariate

Table 11 JAPAN

VENTRAL PROSTATE IN mg

DOSE OF MT (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	0.05	0.5	5	50	Necropsy BODY WT	OVERALL	F VALUE MT	R-SQUARE MT
Lab 15	MEAN	19.3	22.1	26.2	51.1	158.2	289	55.4	70.3	92%
	CV	10	31	16	26	22	5.3	31.1		
11	MEAN	12.6	14.4	21.4	45.3	128.3	295	44.4	49.1	89%
	CV	44	36	36	19	28	4.8	38.3		
13	MEAN	21.1	20.4	18.7	40.6	135	315	47.1	122	95%
	CV	23	15	17	36	14	4.3	23		
16	MEAN	19.2	20.8	19.5	32.3	151	288.4	48.5	59.8	90.50%
	CV	19	24	19	32	26	6	37		
ALL LABS TP=0	MEAN	18	19.4	21.4	42.3	143		48.9		91.80%
	CV	29	29	26	31	23		33		

ANOVA For			p VALUE	R2
MT effect	F=	265	0.0001	89.00%
Lab Effect	F=	2.5	0.06	0.60%
MT*Lab	F=	1.1	0.41	1.10%

TABLE 12 JAPAN SEMINAL VESICLE IN mg

DOSE OF MT (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	0.05	0.5	5	50	Necropsy BODY WT	OVERALL	F VALUE MT	R-SQUARE MT
Lab 15	MEAN	44.2	52.9	66.2	108	313	289	117	28.9	82%
	CV	8.5	45	11	22	35	5.3	44		
11	MEAN	52.5	50.2	48.1	70.7	279	295	100	58.1	90%
	CV	24	14	27	30	24	4.8	32		
13	MEAN	45.2	43.7	43.3	65.7	248	315	89.2	56.7	90%
	CV	13	12	11	27	25	4.3	33		
16	MEAN	39.7	37.3	34.8	41.2	184	288.4	67.4	347	98.20%
	CV	12	14	16	16	8	6	13		
ALL LABS	MEAN	45.4	46	48.1	71.4	256		93.3		90.00%
TP=0	CV	19	30	29	42	32		36		

ANOVA For SV			p VALUE	R2
MT effect	F=	176	0.0001	81.20%
Lab Effect	F=	11.2	0.0001	3.90%
MT*Lab	F=	2.4	0.009	3.40%

Table 13 JAPAN

LABC IN mg

DOSE OF MT (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	0.05	0.5	5	50	Necropsy BODY WT	OVERALL	F VALUE MT	R-SQUARE MT
Lab 15	MEAN	202	204	213	254	482	289	271	46.3	88%
	CV	12	14	14	13	16	5.3	16		
11	MEAN	236	219	229	287	534	295	301	68.2	92%
	CV	17	18	9	7	12	4.8	13		
13	MEAN	192	198	198	253	461	315	260	71.2	92%
	CV	15	10	8	14	11	4.3	13		
16	MEAN	206	200	204	244	487	288.4	268	123	95.20%
	CV	10	16	14	11	5	6	10		
ALL LABS TP=0	MEAN	209	205	211	260	491		275		91.80%
	CV	15	14	12	12	12		13		

ANOVA For LABC			p VALUE	R2
		27		
MT effect	F=	4	0.0001	89.70%
Lab Effect	F=	7.2	0.0002	7.80%
MT*Lab	F=	0.4	0.96	0.40%

Table 14 JAPAN

GLANS PENIS IN mg

DOSE OF MT (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	0.05	0.5	5	50	Necropsy BODY WT	OVERALL	F VALUE MT	R-SQUARE MT
Lab 15	MEAN	62.6	60.8	61.9	74.4	94.7	289	70.9	21.2	77%
	CV	7	6	7.5	13.8	12.2	5.3	10.8		
11	MEAN	48.9	50.8	49.9	55	73.3	295	55.6	29.3	82%
	CV	11.6	6.2	7.9	8.1	7.3	4.8	8.3		
13	MEAN	51.4	55.6	53.4	64.8	83.2	315	61.7	40.5	87%
	CV	5.5	8	9	8.7	7.9	4.3	8.2		
16	MEAN	52.8	53.1	53.7	56.8	83.5	288.4	61.7	131	96.70%
	CV	4.8	5.5	2.8	4.6	3.9	6	4.4		
ALL LABS	MEAN	54	55.2	54.8	63.3	83.7		62.5		85.80%
TP=0	CV	12.5	9.3	11.1	16	12.4		8.7		

ANOVA For GP			p VALUE	R2
MT effect	F=	125	0.0001	68.20%
Lab Effect	F=	41.3	0.0001	16.90%
MT*Lab	F=	1.3	0.24	2.10%

Table 15 JAPAN

COWS IN mg

DOSE OF MT (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	0.05	0.5	5	50	Necropsy BODY WT	OVERALL	F VALUE MT	R-SQUARE MT
Lab 15	MEAN	8.1	7.5	9.5	11.8	22.1	289	11.8	39.9	86%
	CV	17	30	19	26	12	5.3	19.7		
11	MEAN	6.5	6.8	7.6	11	27.2	295	11.8	15.4	71%
	CV	38	22	24	22	42	4.8	46.2		
13	MEAN	6.5	7.8	7.6	10.8	25.3	315	11.6	80.4	93%
	CV	24	22	24	33	4.5	4.3	18.4		
16	MEAN	6.5	7.4	5.8	7.55	26.3	288.4	10.7	73.9	92.20%
	CV	10	11	16	21	20	6	23		
ALL LABS	MEAN	6.9	7.4	7.6	10.3	25.2		11.4		90.50%
TP=0	CV	25	21	27	30	25		30		

ANOVA For COWS		12	p VALUE	R2
MT effect	F=	7	0.0001	81.10%
Lab Effect	F=	0.7	0.56	0.30%
MT*Lab	F=	1.3	0.22	2.50%

Table 16 Ventral Prostate EU | TRENBOLONE (oral gavage) mg/kg/d ten days

DOSE OF FIN (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	0.3	1.5	8	40	Necropsy BODY WT	OVERALL	F VALUE TREN	R-SQUARE TREN	TP=.4 Chem= 0
Lab 7	MEAN	15.2	19.5	16.5	25.3	35.1	304	22.3	7.1	53%	149
TP=0.4	CV	36	28	37	23	19		27			24
3	MEAN	26.3	29.9	32.5	29.4	48.3	238	33.3	1.4	18%	157
TP=0.4	CV	51	53	47	55	47		51			20
1	MEAN	15.8	20	18.8	19.8	37.6	203	22.3	11.1	64%	122
TP=0.4	CV	20	26	19	22	30		28			17
ALL LABS	MEAN	19.1	23	22.5	24.8	40.3				45.00%	
TP=0.4	CV	50	47	52	42	38					

ANOVA For VP			p VALUE	R2
Chemical effect	F=	11.1	p<0.0001	32.00%
Lab Effect	F=	8	p<0.0001	11.00%
Chemical*Lab	F=	0.54	NS	

Data analyzed by SAS using Proc GLM with Log10 transformed data

Table 17 Seminal Vesicle EU TRENBOLONE (oral gavage) mg/kg/d ten days

DOSE OF FIN (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	0.3	1.5	8	40	Necropsy BODY WT	OVERALL	F VALUE TREN	R-SQUARE TREN	TP=.4 Chem= 0
Lab 7	MEAN	95.4	76.5	73.4	93.4	171	304	102	6.6	51%	348
TP=0.4	CV	26	30	25	15	56		46			45
3	MEAN	63	58	77	68	155	238	84.1	8.38	57%	744
TP=0.4	CV	29	16	21	46	46		43			22
1	MEAN	23.2	24.1	26.1	28.1	58	203	31.9	2.85	31%	237
TP=0.4	CV	19	48	33	40	47		46			18
ALL LABS	MEAN	60.6	52.7	58.7	63.1	128				46.00%	
TP=0.4	CV	58	51	47	54	66					

ANOVA For SV			p VALUE	R2
Chemical effect	F=	14	p<.0001	18.00%
Lab Effect	F=	90.5	p<.0001	57.00%
Chemical*Lab	F=	0.47	ns	

Data analyzed by SAS using Proc GLM with Log10 transformed data

Table 18 LABC EU

TRENBOLONE (oral gavage) mg/kg/d ten days

DOSE OF FIN (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	0.3	1.5	8	40	Necropsy BODY WT	OVERALL	F VALUE TREN	R-SQUARE TREN	TP=.4 Chem= 0
Lab 7	MEAN	233	248	260	322	478	304	308	14.1	69%	517
TP=0.4	CV	18	23	20	18	16		18			20
3	MEAN	196	186	219	223	395	238	246	19.6	77%	578
TP=0.4	CV	20	20	14	16	13		16			7
1	MEAN	146	137	147	165	263	203	172	13.2	68%	373
TP=0.4	CV	13	15	18	25	16		18			12
ALL LABS	MEAN	192	191	209	237	379				71.00%	
TP=0.4	CV	26	32	29	33	28					

ANOVA For LABC			p VALUE	R2
Chemical effect	F=	45	p<0.0001	44.00%
Lab Effect	F=	78.4	p<0.0001	37.00%
Chemical*Lab	F=	0.54	ns	

Data analyzed by SAS using Proc GLM with Log10 transformed data

Table 19 Glans Penis EU

TRENBOLONE (oral gavage) mg/kg/d ten days

DOSE OF FIN (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	0.3	1.5	8	40	Necropsy BODY WT	OVERALL	F VALUE TREN	R-SQUARE TREN	TP=.4 Chem= 0
Lab 7	MEAN	70	67.9	65.1	80.9	87.3	304	74.2	10	61%	102
TP=0.4	CV	8	8	16	6	7		9			9
3	MEAN	48.1	48	51.8	51.3	69.5	238	53.8	9.6	60%	82.1
TP=0.4	CV	8	8	11	14	16		13			12
1	MEAN	42.9	41.9	44.7	43	52.2	203	44.9	11.6	65%	68.5
TP=0.4	CV	8	9	12	16	8		28			8
ALL LABS	MEAN	53.6	52.6	53.9	58.4	69.7				62.00%	
TP=0.4	CV	24	23	21	31	24					

ANOVA For SV			p VALUE	R2
Chemical effect	F=	19.2	p<0.0001	16.00%
Lab Effect	F=	158	p<0.0001	66.00%
Chemical*Lab	F=	1.9	ns	

Data analyzed by SAS using Proc GLM with Log10 transformed data

Table 20 Cowper's glands EU

TRENBOLONE (oral gavage) mg/kg/d ten days

DOSE OF FIN (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	0.3	1.5	8	40	Necropsy BODY WT	OVERALL	F VALUE TREN	R-SQUARE TREN	TP=.4 Chem= 0
Lab 7	MEAN	8.2	10.3	8	10	19.6	304	11.2	4	39%	40
TP=0.4	CV	43	60	36	34	46		49			22
3	MEAN	5.7	5.2	7.3	5.5	11.2	238	7	8.81	58%	30.3
TP=0.4	CV	34	24	16	13	22		23			15
1	MEAN	7.2	5.8	6.2	6.6	11.4	203	7.4	4.53	42%	27.6
TP=0.4	CV	37	19	16	27	33		31			15
ALL LABS	MEAN	7	7.1	7.2	7.4	14.1				46.00%	
TP=0.4	CV	63	59	27	39	48					

ANOVA For COWs			p VALUE	R2
Chemical effect	F=	13.6	p<0.0001	33.00%
Lab Effect	F=	12	p<0.0001	15.00%
Chemical*Lab	F=	0.86	ns	

Data analyzed by SAS using Proc GLM with LOG10 transformed data

Table 21 Ventral Prostate EU

VINCLOZOLIN (oral gavage) mg/kg/d ten days

DOSE (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	3	10	30	100	Necropsy BODY WT	OVERALL	F VALUE VIN	R-SQUARE VIN
Lab 1	MEAN	107	104	94.5	79	32.2	222	83.2	32.5	84%
TP=0.4	CV	19	24	13	21	25		21		
3	MEAN	179	183	172	130	83.2	300	150	10.9	63%
TP=0.4	CV	14	31	22	17	14		24		
5	MEAN	132	124	126	110	50.3	287	108	10.3	62%
TP=0.4	CV	27	42	28	18	20		31		
7	MEAN	161	131	131	93	50.7	333	113	17.6	74.00%
TP=0.4	CV	18	24	18	20	46		22		
ALL LABS	MEAN	145	135	131	103	54				71.00%
TP=0.4	CV	27	37	30	26	47				

ANOVA For VP			p VALUE	R2
Chemical effect	F=	62	<.0001	57.00%
Lab Effect	F=	27	<.0001	18.00%
Chemical*Lab	F=	0.8	ns	

Data analysed on SAS using Proc GLM using log10 transformed data

Table 22 Seminal Vesicle EU VINCLOZOLIN (oral gavage) mg/kg/d ten days

DOSE (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	3	10	30	100	Necropsy BODY WT	OVERALL	F VALUE VIN	R-SQUARE VIN
Lab 1	MEAN	217	262	202	143	45	222	174	34.5	85%
TP=0.4	CV	27	38	20	30	23		34		
3	MEAN	764	914	764	533	347	300	665	15.9	72%
TP=0.4	CV	30	17	40	22	14		21		
5	MEAN	547	464	491	341	146	287	398	38.1	86%
TP=0.4	CV	20	12	16	32	20		21		
7	MEAN	420	434	398	280	135	333	333	24	80.00%
TP=0.4	CV	19	11	31	20	35		23		
ALL LABS	MEAN	487	518	464	325	169				81.00%
TP=0.4	CV	49	51	48	51	70				

ANOVA For SV			p VALUE	R2
Chemical effect	F=	107	<.0001	40.00%
Lab Effect	F=	174	<.0001	48.00%
Chemical*Lab	F=	2.2	0.0147	

Data analyzed by SAS using Proc GLM with log10 transformed data

Table 23 LABC EU

VINCLOZOLIN (oral gavage) mg/kg/d ten days

DOSE (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	3	10	30	100	Necropsy BODY WT	OVERALL	F VALUE VIN	R-SQUARE VIN
Lab 1	MEAN	310	337	295	235	160	222	267	32.4	84%
TP=0.4	CV	7	17	15	13	9		13.7		
3	MEAN	653	649	634	482	369	300	557	11.6	65%
TP=0.4	CV	12	28	9	5	6		16		
5	MEAN	467	396	430	352	257	287	380	19	75%
TP=0.4	CV	11	12	14	17	11		13		
7	MEAN	548	501	512	377	282	333	444	25	80.00%
TP=0.4	CV	13	12	18	6	14		14		
ALL LABS	MEAN	495	471	468	361	267				76.00%
TP=0.4	CV	28	33	30	27	30				

ANOVA ForLABC			p VALUE	R2
Chemical effect	F=	78.5	<.0001	37.00%
Lab Effect	F=	140	<.0001	50.00%
Chemical*Lab	F=	0.8	ns	

Data analyzed by SAS using Proc GLM with log10 transformed data

Table 24 GLANS PENIS EU | VINCLOZOLIN (oral gavage) mg/kg/d ten days

DOSE (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	3	10	30	100	Necropsy BODY WT	OVERALL	F VALUE VIN	R-SQUARE VIN
Lab 1	MEAN	66	66	58.3	55.3	42.8	222	57.7	18.4	75%
TP=0.4	CV	6	8	10	13	13		9.8		
3	MEAN	90.7	89.5	84.2	91.8	73.8	300	86	4.9	44%
TP=0.4	CV	9	13	4	12	9		10		
5	MEAN	89.5	86.9	87.1	86.5	75.1	287	86.5	0.8	14%
TP=0.4	CV	15	10	9	9	9		11		
7	MEAN	91.3	91.6	94.3	86.7	74.2	333	87.6	3.9	38.00%
TP=0.4	CV	7	15	11	9	15		12		
ALL LABS	MEAN	84.3	83.5	81	79.8	64.7				43.00%
TP=0.4	CV	16	17	19	21	26				

ANOVA For GP			p VALUE	R2
Chemical effect	F=	20.9	<.0001	16.00%
Lab Effect	F=	107	<.0001	62.00%
Chemical*Lab	F=	1.6	ns	

Data analyzed by SAS using Proc GLM with log10 transformed data

Table 25 COWPER'S GLAND EU | Vinclozolin (oral gavage) mg/kg/d ten days

DOSE (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	3	10	30	100	Necropsy BODY WT	OVERALL	F VALUE VIN	R-SQUARE VIN
Lab 1	MEAN	21.7	25.2	18.7	15	10.7	222	18.2	15.8	72%
TP=0.4	CV	9	29	21	15	24		22		
3	MEAN	31.7	36.4	33.4	29.8	20.7	300	30.4	13.9	69%
TP=0.4	CV	14	21	12	8	14		15		
5	MEAN	34.3	27.2	32.9	25.7	16.4	287	27.3	9.6	61%
TP=0.4	CV	25	21	21	15	33		23		
7	MEAN	36.7	36.2	34.7	42.1	18.2	333	33.6	6	49.00%
TP=0.4	CV	10	8	25	80	27		47		
ALL LABS	MEAN	31.1	31.3	29.9	28.2	16.5				63.00%
TP=0.4	CV	25	25	30	67	33				

ANOVA For COWS			p VALUE	R2
Chemical effect	F=	34.4	<.0001	37%
Lab Effect	F=	39	<.0001	32
Chemical*Lab	F=	1.3	ns	

Data analyzed by SAS using Proc GLM with log10 transformed data

Table 26 ADRENAL GLANDS EU — Vinclozolin (oral gavage) mg/kg/d ten days — Type III SS

DOSE (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	3	10	30	100		OVERALL	F VALUE VIN
Lab 1	MEAN	69.3	63.7	65	77.5	95		74.1	10
TP=0.4	CV	18	15	13	23	14		14.5	
3	MEAN	49.4	59.8	59.7	62.7	62.3		57.6	7.3
TP=0.4	CV	12	15	13	13	22		11	
5	MEAN	60.1	63.9	60.6	69	86.8		68.1	9.6
TP=0.4	CV	11	14	15	12	22		14	
7	MEAN	59.5	56.8	63.7	63.5	71.1		62.9	3.2
TP=0.4	CV	12	17	17	9	11		12	
ALL LABS	MEAN	59.6	59.5	62.2	68.2	78.8			
TP=0.4	CV	18	16	14	18	23			

ANOVA For ADRENALS			p VALUE
Chemical effect	F=	25	0.0001
Lab Effect	F=	29	0.0001
Chemical*Lab	F=	2.6	0.005
Body weight	F=	41	0.0001

Data analyzed by SAS using Proc GLM with untransformed data with body weight covariate

Table 27 LIVER EU

Vinclozolin (oral gavage) mg/kg/d ten days

DOSE (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	3	10	30	100		OVERALL	F VALUE VIN
Lab 1	MEAN	6.55	6.7	6.72	6.73	7.22		6.8	6.2
TP=0.4	CV	4	8	11	14	7		4.7	
3	MEAN	13.2	13	13	13.7	14		13.4	7.8
TP=0.4	CV	13	15	7	7	10		4.6	
5	MEAN	10.4	10.5	10.7	11.1	12.1		10.9	5.7
TP=0.4	CV	11	10	10	6	9		7.7	
7	MEAN	15.9	17.4	17.9	17.9	18.2		17.4	3.4
TP=0.4	CV	9	5	11	9	6		6	
ALL LABS	MEAN	11.5	11.9	12.1	12.4	12.9			
TP=0.4	CV	32	35	35	35	32			

ANOVA For LIVER		Type III SS	p VALUE
Chemical effect	F=	16.1	0.0001
Lab Effect	F=	66.1	0.0001
Chemical*Lab	F=	1.1	ns
Body weight	F=	123	0.0001

Data analyzed by SAS using Proc GLM with untransformed data with body weight covariate

Table 28 JAPAN VENTRAL PROSTATE WEIGHT IN mg

DOSE OF Vinclozolin (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	3	10	30	100	Necropsy BODY WT	OVERALL	F VALUE vinclozolin	R-SQUARE vinclozolin	TP=0 VIN=0
Lab 10	MEAN	106	99	84	75	39	289	81	19.3	75.5	14.4
TP=0.2	CV	13	21	16	1.7	34	3.8	17.6			20
11	MEAN	97	112	105	79	34	323	85	15.4	71	19.5
TP=0.2	CV	44	16	18	19	32	4.3	27.8			28
13	MEAN	137	119	91	61	36	339	92	37.5	86	18.7
TP=0.2	CV	25	11	25	14	27	4.6	22			11.8
14	MEAN	184	150	137	98	51	337	124	76	92	28.6
TP=0.2	CV	12	11	11	11	20	2.7	12			26
ALL LABS	MEAN	131	120	104	78	69		95		81.3	
TP=0.2	CV	34	21	25	21	34		20			

ANOVA For VP		TP=0.2	p<	R2
Vinclozolin effect	F=	102	0.0001	69.00%
Lab Effect	F=	21	0.0001	11.00%
vin*Lab	F=	1.8	0.06	3.60%

using log10 transformed data

Table 29 JAPAN SEMINAL VESICLE WEIGHT IN mg

DOSE OF Vinclozolin (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	3	10	30	100	Necropsy BODY WT	OVERALL	F VALUE vinclozolin	R2 vinclozolin	TP=0 VIN=0
Lab 10	MEAN	217	222	168	116	47	289	154	54.3	89.6%	22.2
TP=0.2	CV	18	7.5	25	18	32	3.8	19			16
11	MEAN	362	336	321	211	72	323	260	66.4	91.3%	45.5
TP=0.2	CV	21	16	11	27	23	4.3	20			22
13	MEAN	394	359	249	175	61	340	248	117	94.9%	43.9
TP=0.2	CV	13	13	18	18	21	4.6	18			12
14	MEAN	421	459	344	248	96	337	314	49	89.0%	66.6
TP=0.2	CV	22	22	14	28	17	2.7	23			15
ALL LABS	MEAN	348	344	271	187	69		244		91.2%	
TP=0.2	CV	29	30	30	36	34		21			

ANOVA For SV		F	p<	R2
Vinclozolin effect	F=	264	0.0001	78.50%
Lab Effect	F=	65	0.0001	14.50%
vin*Lab	F=	1	0.41	1.00%

Table 30 JAPAN LABC WEIGHT IN mg

DOSE OF Vinclozolin (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	3	10	30	100	Necropsy BODY WT	OVERALL	F VALUE vinclozolin	R-SQUARE vinclozolin	TP=0 VIN=0
Lab 10	MEAN	361	321	324	268	182	289	291	24.6	79.7%	148
TP=0.2	CV	13	13	6	9	19	3.8	12			12
11	MEAN	538	501	485	416	275	323	443	21	77.0%	226
TP=0.2	CV	17	16	14	13	9	4.3	15			7.9
13	MEAN	534	511	442	382	258	340	429	42	87.0%	217
TP=0.2	CV	4.9	4.9	7.5	13	20	4.6	10			8.1
14	MEAN	590	609	529	431	309	337	494	41	87.0%	288
TP=0.2	CV	8.9	16	10	7.6	10	2.7	12			8.4
ALL LABS	MEAN	506	485	445	374	256		413		82.8%	
TP=0.2	CV	21	25	20	20	23		12.5			

ANOVA For LABC		TP=0.2	p<	R2
Vinclozolin effect	F=	118	0.0001	54.00%
Lab Effect	F=	100	0.0001	34.40%
vin*Lab	F=	0.53	0.89	1.00%

using log10 transformed data

Table 31 JAPAN GLANS PENIS WEIGHT IN mg

DOSE OF Vinclozolin (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	3	10	30	100	Necropsy BODY WT	OVERALL	F VALUE vinclozolin	R-SQUARE vinclozolin	TP=0 VIN=0
Lab 10	MEAN	70	70	67.3	64.7	51.4	289	64.7	19.2	75.30%	39.10%
TP=0.2	CV	5.5	2.8	5.9	6.9	12.8	3.8	6.9			7.1
11	MEAN	81.7	75.9	73.7	69.8	58.5	323	71.9	9.9	62.1%	49.4
TP=0.2	CV	11	8	7.5	10.3	8.8	4.3	9.4			4.7
13	MEAN	91.1	88.9	79.8	76.8	64	340	81.3	40	86.0%	55.5
TP=0.2	CV	6.3	5	5.6	5.7	4.5	4.6	5.6			4.8
14	MEAN	76.4	78	77.7	70.2	52.7	337	71	17	74.00%	48.7
TP=0.2	CV	9.9	14.4	5.7	11	4.9	2.7	9.8			11.0
ALL LABS	MEAN	79.8	78.2	74.7	70.4	56.7		71.9		74.20%	
TP=0.2	CV	12.7	12.1	8.8	9.7	11.8		8			

ANOVA For GP		TP=0.2	p<	R2
Vinclozolin effect	F=	70	0.0001	56.50%
Lab Effect	F=	36	0.0001	21.00%
vin*Lab	F=	1.1	0.37	

Table 32 JAPAN COWS WEIGHT IN mg

DOSE OF Vinclozolin (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	3	10	30	100	Necropsy BODY WT	OVERALL	F VALUE vinclozolin	R2 vinclozolin	TP=0 VIN=0
lab 10	MEAN	20.8	21.1	19.5	15.1	7.4	289	16.8	34.2	85	4.3
TP=0.2	CV	6.2	24.8	18	19	24	3.8	19.4			19
11	MEAN	28	26.8	21.1	20.1	11.2	323	21.4	18	74	6.4
TP=0.2	CV	22	11	27	11.9	17.3	4.3	19.7			30
13	MEAN	32.7	32.7	24.3	20.2	12.4	340	24.7	25	80	6.7
TP=0.2	CV	18	16	27	15	20	4.6	19.4			15
14	MEAN	38.6	36	32.9	25.9	16.2	337	29.9	17	73	11.4
TP=0.2	CV	11	21	16	22	35	2.7	19			32
ALL LABS	MEAN	30	29.2	24.5	20.3	11.8		23.2		78	
TP=0.2	CV	27	26	29.6	25	38		19.9			

ANOVA For COWS		TP=0.2	p<	R2
Vinclozolin effect	F=	88	0.0001	59.40%
Lab Effect	F=	44	0.0001	22.10%
vin*Lab	F=	0.8	0.68	

Using log 10 transformed data

Table 33 Ventral Prostate EU | PROCYMIDONE (oral gavage) mg/kg/d ten days

DOSE (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	3	10	30	100	Necropsy BODY WT	OVERALL	F VALUE PRO	R-SQUARE PRO
Lab 2	MEAN	174	180	151	103	53	301	132	18.8	74%
TP=0.4	CV	19	24	35	16	45		27		
7	MEAN	157	140	104	80.4	57.9	316	108	10.4	62%
TP=0.4	CV	11	35	32	32	34		29		
8	MEAN	212	194	145	130	68.2	321	150	98	88%
TP=0.4	CV	9	15	18	13	20		14		
9	MEAN	146	139	119	112	76	334	118	22.6	78.00%
TP=0.4	CV	11	13	15	15	12		13		
ALL LABS	MEAN	180	170	132	111	65				75.50%
TP=0.4	CV	19	25	28	24	28				

ANOVA For VP		10	p VALUE	R2
Chemical effect	F=	1	<.0001	67.00%
Lab Effect	F=	16	<.0001	8.00%
Chemical*Lab	F=	2.2	<.014	

Data analysed on SAS using Proc GLM using transformed data

Table 34 Seminal Vesicle EU | PROCYMIDONE (oral gavage) mg/kg/d ten days

DOSE (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	3	10	30	100	Necropsy BODY WT	OVERALL	F VALUE PRO	R-SQUARE PRO
Lab 2	MEAN	356	362	406	216	146	301	298	9.2	59%
TP=0.4	CV	15	13	43	27	48		32		
7	MEAN	485	475	397	224	206	316	357	20.4	77%
TP=0.4	CV	8	22	12	22	37		19		
8	MEAN	637	596	491	396	201	321	464	71	84%
TP=0.4	CV	18	16	13	12	27		17		
9	MEAN	489	446	403	282	255	334	375	59	90.00%
TP=0.4	CV	11	9	8	10	8		10		
ALL LABS	MEAN	521	495	434	303	202				77.50%
TP=0.4	CV	26	24	23	31	32				

ANOVA For SV			p VALUE	R2
Chemical effect	F=	95	<.0001	61.00%
Lab Effect	F=	28	<.0001	14.00%
Chemical*Lab	F=	2.5	<.01	

Data analyzed by SAS using Proc GLM with transformed data

Table 35 LABC EU

PROCYMIDONE (MG/KG/D)

DOSE (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	3	10	30	100	Necropsy BODY WT	OVERALL	F VALUE PRO	R-SQUARE PRO
Lab 2	MEAN	293	340	322	278	204	301	287	8.2	57%
TP=0.4	CV	14	10	25	14	16		17		
7	MEAN	542	515	468	325	333	316	436	4.1	40%
TP=0.4	CV	12	9	25	40	19		21		
8	MEAN	655	616	558	396	319	321	521	96	88%
TP=0.4	CV	10	9	10	12	12		10		
9	MEAN	394	355	338	275	252	334	323	30	83.00%
TP=0.4	CV	8	9	9	9	7		8		
ALL LABS	MEAN	508	488	441	362	285				67.00%
TP=0.4	CV	31	27	28	30	22				

ANOVA ForLABC			p VALUE	R2
Chemical effect	F=	11	<.0001	33.00%
Lab Effect	F=	83	<.0001	41.00%
Chemical*Lab	F=	2.6	<.01	

Data analyzed by SAS using Proc GLM with transformed data

Table 36 GLANS PENIS EU | PROCYMIDONE (oral gavage) mg/kg/d ten days

DOSE (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	3	10	30	100	Necropsy BODY WT	OVERALL	F VALUE PRO	R-SQUARE PRO
Lab 2	MEAN	79.1	83.2	85.6	79.7	66.6	301	78.8	1.9	23%
TP=0.4	CV	6.2	24	9	14	28		17		
7	MEAN	91.7	98.9	85.3	78.5	81.2	316	56.7	3.3	34%
TP=0.4	CV	17	13	5	11	9		12		
8	MEAN	92.1	85.3	82.9	76.4	65.6	321	80.3	17.4	57%
TP=0.4	CV	10	10	10	9	15		11		
9	MEAN	124	115	113	109	108	334	114	3.24	34.00%
TP=0.4	CV	11	7	6	6	5		7		
ALL LABS	MEAN	95.8	93.2	90.5	83.9	77.4				37.00%
TP=0.4	CV	19	18	15	18	25				

ANOVA For GP			p VALUE	R2
Chemical effect	F=	16	<.0001	16.00%
Lab Effect	F=	62	<.0001	47.00%
Chemical*Lab	F=	1.7	NS	

Data analyzed by SAS using Proc GLM with transformed data

Table 37 COWPER'S GLAND EU | PROCYMIDONE (oral gavage) mg/kg/d ten days

DOSE (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	3	10	30	100	Necropsy BODY WT	OVERALL	F VALUE PRO	R-SQUARE PRO
Lab 2	MEAN	32.7	30.4	31.4	29.1	15.6	301	27.8	6.3	50%
TP=0.4	CV	24	27	28	49	32		34		
7	MEAN	36.8	34.6	29.5	22.3	21.5	316	30	4.9	44%
TP=0.4	CV	28	26	32	12	30		28		
8	MEAN	48.2	45.2	37.4	35.6	21.8	321	37.6	28	68%
TP=0.4	CV	17	15	23	28	21		21		
9	MEAN	40.1	35.4	31.6	26.1	20.8	334	30.8	57	90.00%
TP=0.4	CV	8	7	7	9	9		8.2		
ALL LABS	MEAN	41.2	38.2	33.2	29.8	20.3				63.00%
TP=0.4	CV	24	24	25	34	25				

ANOVA For COWS			p VALUE	R2
Chemical effect	F=	46	<.0001	49.00%
Lab Effect	F=	17	<.0001	13.00%
Chemical*Lab	F=	1.1	NS	

Data analyzed by SAS using Proc GLM with transformed data

Table 38 ADRENAL GLANDS EU | PROCYMIDONE (oral gavage) mg/kg/d ten days

DOSE (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	3	10	30	100		OVERALL	F VALUE PRO
Lab 2	MEAN	54	63.4	61.9	66.2	80.6		65.2	5.2
TP=0.4	CV	17	11	16	9	17		16	
7	MEAN	57.8	57.7	61.8	66.3	64.9		61.7	1.9
TP=0.4	CV	9	13	13	11	11		11	
8	MEAN	54.2	49.5	56.1	58.8	66		56.9	9.2
TP=0.4	CV	12	11	13	12	13		12	
9	MEAN	56.6	56.7	53.5	61.3	67.2		59.1	1.9
TP=0.4	CV	8	9	20	23	17		17	
ALL LABS	MEAN	55.3	55.4	58	62.3	68.9			
TP=0.4	CV	12	17	15	14	16			

ANOVA For Adrenals			p VALUE	
Chemical effect	F=	14.3	0.0001	
Lab Effect	F=	8.8	0.0001	
Chemical*Lab	F=	1.4	ns	
Body weight		F=	5.4	0.025

Data analyzed by SAS using Proc GLM with untransformed data and body weight as a covariate

Table 39 LIVER EU

PROCYMIDONE (oral gavage) mg/kg/d ten days

Type III SS

DOSE (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	3	10	30	100		OVERALL	F VALUE PRO
Lab 2	MEAN	13.4	13.1	12.5	13.8	13.9		13.3	3.6
TP=0.4	CV	6	6	8	12	6		5.7	
7	MEAN	16.3	17.4	17.9	18.9	20.2		18.1	11.2
TP=0.4	CV	10	11	11	14	3		7	
8	MEAN	13.5	13.5	13.2	13.3	14.1		13.6	4.7
TP=0.4	CV	9	8	5	5	9		6	
9	MEAN	17.2	16.3	16.8	18	18.4		17.3	12.1
TP=0.4	CV	8	6	5	6	9		4	
ALL LABS	MEAN	14.8	14.8	14.8	15.4	16.2			
TP=0.4	CV	14	14	17	18	18			

ANOVA For LIVER			p VALUE
Chemical effect	F=	26.5	0.0001
Lab Effect	F=	205	0.0001
Chemical*Lab	F=	3.9	0.0001
Body weight	F=	107	0.000 1

Data analyzed by SAS using Proc GLM with untransformed data and body weight as a covariate

Table 40 Ventral Prostate EU | p,p' DDE (oral gavage) mg/kg/d ten days

DOSE OF FIN (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	5	16	50	160	Necropsy BODY WT	OVERALL	F VALUE DDE	R-SQUARE DDE
Lab 3	MEAN	153	156	147	94	40	255	118	24	79%
TP=0.4	CV	11	21	13	23	57		20		
Lab 4	MEAN	184	166	202	159	91	363	163	5.4	47%
TP=0.4	CV	44	14	24	22	30		30		
Lab 8	MEAN	210	200	196	163	78	318	169	38	86%
TP=0.4	CV	11	12	13	16	28		14		
Lab 9	MEAN	144	124	123	106	71	329	114	9.5	60.00%
TP=0.4	CV	16	11	30	4	11		19		
ALL LABS	MEAN	173	160	162	122	64				68.00%
TP=0.4	CV	29	25	30	38	46				

ANOVA For VP			p VALUE	R2
Chemical effect	F=	57	0.0001	54.00%
Lab Effect	F=	22	0.0001	15.00%
Chemical*Lab	F=	3	0.0013	

Data analyzed by SAS using Proc GLM with log10 transformed data

Table 41 Seminal Vesicle EU | p,p' DDE (oral gavage) mg/kg/d ten days

DOSE OF FIN (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	5	16	50	160	Necropsy BODY WT	OVERALL	F VALUE DDE	R-SQUARE DDE
3	MEAN	539	601	524	402	128	255	438	36	85%
TP=0.4	CV	14	22	16	24	42		21		
4	MEAN	551	599	594	483	310	363	515	3.8	39%
TP=0.4	CV	33	31	20	40	35		32		
8	MEAN	694	590	701	461	214	318	530	46	89%
TP=0.4	CV	11	18	19	16	21		17		
9	MEAN	475	424	396	383	229	329	381	23	79.00%
TP=0.4	CV	8	17	20	10	11		14		
ALL LABS	MEAN	565	545	550	394	193				73.00%
TP=0.4	CV	24	28	27	38	50				

ANOVA For SV			p VALUE	R2
Chemical effect	F=	74	0.0001	65.00%
Lab Effect	F=	11	0.0001	7.10%
Chemical*Lab	F=	4	0.0001	

Data analyzed by SAS using Proc GLM withlog10 transformed data

Table 42 LABC EU

p,p' DDE (oral gavage) mg/kg/d ten days

DOSE OF FIN (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	5	16	50	160	Necropsy BODY WT	OVERALL	F VALUE DDE	R-SQUARE DDE
3	MEAN	529	498	451	370	194	255	409	49	89%
TP=0.4	CV	16	15	6	11	19		14		
4	MEAN	635	617	619	525	338	363	554	30.5	83%
TP=0.4	CV	11	12	8	11	13		11		
8	MEAN	656	580	606	510	341	318	537	17	74%
TP=0.4	CV	12	5	9	7	32		13		
9	MEAN	372	373	340	315	231	329	326	22	78.00%
TP=0.4	CV	8	12	8	9	15		10		
ALL LABS	MEAN	548	506	498	409	268				81.00%
TP=0.4	CV	24	24	27	31	36				

ANOVA For LABC			p VALUE	R2
Chemical effect	F=	109	0.0001	49.00%
Lab Effect	F=	105	0.0001	36.00%
Chemical*Lab	F=	2.9	0.01	

Data analyzed by SAS using Proc GLM with log10 transformed data

Table 43 GLANS PENIS EU p,p' DDE (oral gavage) mg/kg/d ten days

DOSE OF FIN (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	5	16	50	160	Necropsy BODY WT	OVERALL	F VALUE DDE	R-SQUARE DDE
LAB 3	MEAN	80.1	81	76	72.8	53.8	255	73	12.5	67%
TP=0.4	CV	13	12	8	11	15		12		
4	MEAN	101	101	107	100	83	363	99	2.7	31%
TP=0.4	CV	6	17	7	14	16		12		
8	MEAN	97	84.5	92.6	87	68	318	87	9.3	62%
TP=0.4	CV	8	4	10	7	18		10		
9	MEAN	111	111	112	106	88.3	329	105	11.5	65.00%
TP=0.4	CV	4	10	9	4	8		7		
ALL LABS	MEAN	97	95	95	87	71.4				56.00%
TP=0.4	CV	14	18	15	15	22				

ANOVA For GP			p VALUE	R2
Chemical effect	F=	29	0.0001	27.00%
Lab Effect	F=	68	0.0001	48.00%
Chemical*Lab	F=	0.98	ns	

Data analyzed by SAS using Proc GLM with log10 transformed data

Table 44 COWPER'S GLANDS EU p,p' DDE (oral gavage) mg/kg/d ten days

DOSE OF FIN (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	5	16	50	160	Necropsy BODY WT	OVERALL	F VALUE DDE	R-SQUARE DDE
Lab 3	MEAN	29.3	27.4	23.4	17.3	10.7	255	21.6	29	82%
TP=0.4	CV	17	6	18	15	27		16		
4	MEAN	45.3	45.7	42.8	33.2	28	363	39	9.2	61%
TP=0.4	CV	15	13	13	25	21		17		
8	MEAN	50.8	51.6	46.1	40.8	27	318	43	11.8	66%
TP=0.4	CV	19	20	12	24	17		19		
9	MEAN	36.7	33.8	31.4	29.4	19.1	329	30.1	15.7	72.00%
TP=0.4	CV	8	16	23	14	12		16		
ALL LABS	MEAN	40.5	38.5	35.4	27.6	19.4				70.00%
TP=0.4	CV	26	31	30	42	47				

ANOVA For COWS			p VALUE	R2
Chemical effect	F=	62	0.0001	37.00%
Lab Effect	F=	100	0.0001	48.00%
Chemical*Lab	F=	1.9	0.05	

Data analyzed by SAS using Proc GLM with log10 transformed data

Table 45 ADRENAL EU

p,p' DDE (oral gavage) mg/kg/d ten days

type III SS

DOSE OF FIN (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	5	16	50	160		OVERALL adj-BWT	F VALUE DDE
Lab 3	MEAN	44.8	43.2	44.4	45.6	51		45.8	5.24
TP=0.4	CV	16	18	9	8	16		11	
4	MEAN	57.2	56.9	56.1	52.2	59.3		56.4	1
TP=0.4	CV	14	16	9	10	12		12	
8	MEAN	51.2	59	55.2	50.5	55.6		54.1	1.2
TP=0.4	CV	13	6	11	19	20		14	
9	MEAN	54.4	57.9	60.4	65.2	58.7		59.3	2.6
TP=0.4	CV	14	10	7	6	11		10	
ALL LABS	MEAN	51.9	54	54	53.4	56			
TP=0.4	CV	16	17	14	18	15			

ANOVA For ADRENAL			p VALUE	R2	
Chemical effect	F=	3.5	0.01	6.70%	
Lab Effect	F=	6.1	0.001	8.60%	
Chemical*Lab	F=	1.7	ns		
Body weight	F=	16.1	0.000 1	7.6	

Data analyzed by SAS using Proc GLM with UNtransformed data WITH BWT AS COVARIATE

Table 46 LIVER EU

p,p' DDE (oral gavage) mg/kg/d ten days

DOSE OF FIN (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	5	16	50	160		OVERALL adj-BWT	F VALUE DDE
3	MEAN	12.2	12.9	15.4	16.7	18		15	44.5
TP=0.4	CV	8	18	11	14	16		7.2	
4	MEAN	15.7	15.5	18.2	19.6	23.1		18.3	68
TP=0.4	CV	14	5	14	8	11		5.4	
8	MEAN	13.9	14.7	16	19	20.6		16.9	23
TP=0.4	CV	9	5	7	4	14		9	
9	MEAN	16	17.2	18.6	23.1	25.7		20.1	75
TP=0.4	CV	10	7	7	5	13		6.1	
ALL LABS	MEAN	14.5	15.1	17.1	19.6	21.8			
TP=0.4	CV	14	14	13	14	19			

ANOVA For LIVER		F	p VALUE	R2	
Chemical effect	F=	185	0.0001	64.00%	
Lab Effect	F=	44	0.0001	11.00%	
Chemical*Lab	F=	1.5	ns		
Body weight		F=	137	0.0001	12

Data analyzed by SAS using Proc GLM with UNtransformed data WITH BWT AS COVARIATE

Table 47 JAPAN

VENTRAL PROSTATE WEIGHT IN mg

DOSE OF p,p' DDE (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	3	10	30	100	Necropsy BODY WT	OVERALL	F VALUE	R-SQUARE DDE	TP=0 DDE=0
Lab 10	MEAN	106	90	100	72	52	273	84	18.2	74.50%	14
TP=0.2	CV	12	7	18	19	16	3.7	15			15
11	MEAN	138	126	129	94	51	312	107	11.5	64.80%	25
TP=0.2	CV	25	21	17	28	32	4.7	24			63
12	MEAN	91	79	88	90	57	239	81	8.2	56.80%	8.2
TP=0.2	CV	18	10	17	14	12	3.2	15			60
14	MEAN	153	158	166	142	78	320	139	7.7	55.00%	23
TP=0.2	CV	13	26	26	12	36	3.4	23			22
16	MEAN	115	101	103	75	49	291	89	11.5	64.70%	17
TP=0.2	CV	16	27	16	24	25	6	22			9
ALL LABS	MEAN	121	111	117	94	57		100		63.00%	
TP=0.2	CV	25	34	31	33	32		22			

ANOVA For VP		TP=0.2	p<	R2
DDE effect	F=	43.3	0.0001	36.10%
Lab Effect	F=	37.9	0.0001	31.70%
DDE*Lab	F=	1.8	0.04	6.10%

Table 48 JAPAN

SEMINAL VESICLE WEIGHT IN mg

DOSE OF p,p' DDE (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	3	10	30	100	Necropsy BODY WT	OVERALL	F VALUE DDE	R-SQUARE DDE	TP=0 DDE=0
Lab 10	MEAN	226	219	202	164	75	273	177	23.8	79%	51
TP=0.2	CV	22	13	7	22	16	3.7	18			117
11	MEAN	387	272	377	256	88	312	276	33.1	84%	50
TP=0.2	CV	16	8	13	27	48	4.7	19			33
12	MEAN	283	246	240	232	152	239	231	10.2	62%	38
TP=0.2	CV	12	20	11	17	21	3.3	16			20
14	MEAN	371	433	412	324	148	320	337	21.5	77.50%	70
TP=0.2	CV	15	11	15	2	32	3.4	18			9
16	MEAN	237	219	251	157	83	291	190	22.7	78.30%	34
TP=0.2	CV	11	19	19	21	28	6	19			10
ALL LABS	MEAN	301	278	297	227	109		242	97.3	45.30%	
TP=0.2	CV	27	32	31	36	42		18			

ANOVA For SV		TP=0.2	p<	R2
DDE effect	F=	97.3	0.0001	45.30%
Lab Effect	F=	66.3	0.0001	30.90%
DDE*Lab	F=	5	0.0001	9.30%

Table 49 JAPAN

LABC WEIGHT IN mg

DOSE OF p,p' DDE (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	3	10	30	100	Necropsy BODY WT	OVERALL	F VALUE DDE	R-SQUARE DDE	TP=0 DDE=0
Lab 10	MEAN	300	306	290	309	210	273	283	8	56%	144
TP=0.2	CV	10	7	12	19	8	3.7	13			18
11	MEAN	550	522	519	459	300	312	470	22.9	79%	209
TP=0.2	CV	7	12	11	13	10	4.7	11			12
12	MEAN	436	430	407	408	312	239	398	6	49%	167
TP=0.2	CV	17	12	3.7	14	9	3.3	12.5			18
14	MEAN	518	574	547	490	291	320	484	53	89.00%	260
TP=0.2	CV	2	7	7	11	11	3.4	8			9
16	MEAN	496	497	451	395	302	291	428	16.4	72.30%	196
TP=0.2	CV	16	6	11	8	14	6	12			14
ALL LABS	MEAN	460	466	443	412	283		413		69.00%	
TP=0.2	CV	22	22	23	19	17		11			

ANOVA For LABC			p VALUE	R2
DDE effect	F=	82.7	0.0001	37.20%
Lab Effect	F=	93.2	0.0001	41.90%
DDE*Lab	F=	3.8	0.0001	6.80%

Table 50 JAPAN

GLANS PENIS IN mg

DOSE OF p,p' DDE (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	3	10	30	100	Necropsy BODY WT	OVERALL	F VALUE DDE	R-SQUARE DDE	TP=0 DDE=0
Lab 10	MEAN	67	62.3	66.3	65	56.6	273	63.4	6.9	38%	40.1
TP=0.2	CV	6.6	8.2	4.6	8.3	13.2	3.7	8.4			8
11	MEAN	73.3	76.5	73.5	73.6	63	312	92	15.8	72%	51
TP=0.2	CV	3.7	5.1	3.7	4.7	4.8	4.7	4.4			10
12	MEAN	65.5	64.9	63.8	66.9	52	239	62.6	3.9	38%	33.6
TP=0.2	CV	13	5.6	9.1	10	21	3.3	12.1			34
14	MEAN	77.3	75.9	76.5	74	60.8	320	72.9	15.1	70.70%	51.6
TP=0.2	CV	5	6.4	7.4	5.8	3.5	3.4	5.9			9.5
16	MEAN	81	80.1	77.6	76.2	66.7	291	76.3	6.5	51.10%	50.6
TP=0.2	CV	8.4	4.1	6.2	6.6	10	6	7.2			6.6
ALL LABS	MEAN	72.8	71.9	71.5	71.1	59.8		69.4		54.00%	
TP=0.2	CV	11	11.3	9.9	9.1	14		7.7			

ANOVA For GP			p VALUE	R2
DDE effect	F=	30.7	0.0001	29.70%
Lab Effect	F=	38.6	0.0001	37.30%
DDE*Lab	F=	0.7	0.76	2.80%

Table 51 JAPAN COWS IN mg

DOSE OF p,p' DDE (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	3	10	30	100	Necropsy BODY WT	OVERALL	F VALUE DDE	R-SQUARE DDE	TP=0 DDE=0
Lab 10	MEAN	21	21.5	19.8	15.4	11	273	17.7	19.8	76%	4.4
TP=0.2	CV	11	14	6.4	19	20	3.7	14			18
11	MEAN	27.2	21.8	28.3	23.7	17.4	312	23.7	3.6	37%	5.9
TP=0.2	CV	26	20	17	30	23	4.7	24			22
12	MEAN	26.2	26.7	25.4	25.9	17	239	24.2	7.7	55%	5.1
TP=0.2	CV	15	18	11	13	13	3.2	15			26
14	MEAN	33.9	33.7	32.8	32.6	20.2	320	30.7	5	44.50%	11
TP=0.2	CV	19	16	13	28	29	3.4	21			22
16	MEAN	30.2	28	25.5	24.2	12.3	291	24	13	67.40%	6.2
TP=0.2	CV	15	18	17	25	26	6	20			28
ALL LABS	MEAN	27.7	26.4	26.4	24.4	15.6		24.1		56.00%	
TP=0.2	CV	24	24	21	33	31		20			

ANOVA For COWS			p VALUE	R2
DDE effect	F=	31.3	0.0001	32.90%
Lab Effect	F=	27.4	0.0001	28.90%
DDE*Lab	F=	1.2	0.25	5.20%

Table 52 Ventral Prostate EU | Linuron (oral gavage) mg/kg/d ten days

DOSE OF LINURON (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	3	10	30	100	Necropsy BODY WT	OVERALL	F VALUE LINURON	R-SQUARE LINURON
Lab 1	MEAN	107	113	123	89	61	216	98	13	67%
TP=0.4	CV	19	15	20	23	18		19		
4	MEAN	167	193	203	184	99	355	169	12	67%
TP=0.4	CV	21	18	17	21	27		20		
5	MEAN	114	112	112	84	46	278	95	18	74%
TP=0.4	CV	19	13	15	25	24		19		
6	MEAN	83	109	115	110	68	303	97	2.1	26.00%
TP=0.4	CV	41	47	22	23	28		35		
ALL LABS	MEAN	118	132	139	117	69				58.50%
TP=0.4	CV	35	36	33	45	47				

ANOVA For VP			p VALUE	R2
Chemical effect	F=	27	0.0001	32.00%
Lab Effect	F=	37	0.0001	33.00%
Chemical*Lab	F=	1.5	0.12	

Data analysed on SAS using Proc GLM using log10 transformed data

Table 53 Seminal Vesicle EU Linuron (oral gavage) mg/kg/d ten days

DOSE OF LINURON (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	3	10	30	100	Necropsy BODY WT	OVERALL	F VALUE LINURON	R-SQUARE LINURON
Lab 1	MEAN	217	293	265	192	102	216	214	25	80%
TP=0.4	CV	27	19	16	18	11	6.4	20		
4	MEAN	485	569	536	541	293	355	485	10	61%
TP=0.4	CV	14	30	15	19	25		22		
5	MEAN	436	389	339	248	141	278	316	20	77%
TP=0.4	CV	22	17	21	18	29		21		
6	MEAN	372	412	395	323	256	303	350	4.2	41.00%
TP=0.4	CV	37	22	21	14	23		26		
ALL LABS	MEAN	377	416	383	326	200				65.00%
TP=0.4	CV	31	34	32	45	47				

ANOVA For SV			p VALUE	R2
Chemical effect	F=	49	0.0001	35.00%
Lab Effect	F=	77	0.0001	41.00%
Chemical*Lab	F=	3	0.01	

Data analyzed by SAS using Proc GLM with log10 transformed data

Table 54 LABC EU

Linuron (oral gavage) mg/kg/d ten days

DOSE OF LINURON (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	3	10	30	100	Necropsy BODY WT	OVERALL	F VALUE LINURON	R-SQUARE LINURON
Lab 1	MEAN	310	368	333	287	188	216	297	17	73%
TP=0.4	CV	7	9	15	17	24	6.4	14		
4	MEAN	651	655	631	571	438	355	589	13	67%
TP=0.4	CV	13	14	8	10	9		12		
5	MEAN	377	351	350	297	158	278	312	36	86%
TP=0.4	CV	11	2	16	8	21		12		
6	MEAN	478	486	492	496	428	303	475	2.2	27.00%
TP=0.4	CV	11	12	6	9	10		9.8		
ALL LABS	MEAN	454	465	450	413	309				63.00%
TP=0.4	CV	31	29	30	32	44				

ANOVA ForLABC			p VALUE	R2
Chemical effect	F=	5820	0.0001	22.00%
Lab Effect	F=	9	0.0001	60.00%
Chemical*Lab	F=	6.2	0.0001	

Data analyzed by SAS using Proc GLM with log10 transformed data

Table 55 GLANS PENIS EU | Linuron (oral gavage) mg/kg/d ten days

DOSE OF LINURON (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	3	10	30	100	Necropsy BODY WT	OVERALL	F VALUE LINURON	R-SQUARE LINURON
Lab 1	MEAN	66	68	65.8	61.5	55	216	63.3	4	41%
TP=0.4	CV	7	13	10	10	9	6.4	10		
4	MEAN	91.2	94.4	102	101	89.4	355	96	1.6	20%
TP=0.4	CV	7	15	11	5	19		12		
5	MEAN	73.2	75	73.8	79	64	278	74	2.3	29%
TP=0.4	CV	9	11	9	10	6		10		
6	MEAN	95.7	93.4	85.1	98	92.7	303	93.2	0.78	12.00%
TP=0.4	CV	13	13	16	5	21		14		
ALL LABS	MEAN	81.5	82.7	81.6	84.9	77				25.50%
TP=0.4	CV	18	19	21	20	28				

ANOVA For GP			p VALUE	R2
Chemical effect	F=	3.5	0.011	3.80%
Lab Effect	F=	81	0.0001	66.00%
Chemical*Lab	F=	1.3	0.23	

Data analyzed by SAS using Proc GLM with log10 transformed data

Table 56 COWPER'S GLAND EU

Linuron (oral gavage) mg/kg/d ten days

DOSE OF LINURON (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	3	10	30	100	Necropsy BODY WT	OVERALL	F VALUE LINURON	R-SQUARE LINURON
Lab 1	MEAN	21.7	30.2	24.2	23.3	15.1	216	22.9	13	67%
TP=0.4	CV	9	24	9	24	10	6.4	19		
4	MEAN	43.1	37.8	43.8	40.5	31.6	355	39.4	3.8	38%
TP=0.4	CV	17	19	15	11	18		16		
5	MEAN	24.9	23.1	24.7	19.5	12.1	278	21.1	10.4	64%
TP=0.4	CV	19	18	25	21	35		22		
6	MEAN	24.1	25.3	24.6	23.3	24.6	303	24.4	0.15	2.50%
TP=0.4	CV	23	12	14	24	35		23		
ALL LABS	MEAN	28.4	29.1	29.5	26.7	21.2				43.00%
TP=0.4	CV	35	27	33	36	44				

ANOVA For COWS			p VALUE	R2
Chemical effect	F=	15	0.0001	16.00%
Lab Effect	F=	60	0.0001	49.00%
Chemical*Lab	F=	2.9	0.002	

Data analyzed by SAS using Proc GLM with log10 transformed data

Table 57 VENTRAL PROSTATE EU FINASTERIDE (oral gavage) mg/kg/d ten days

DOSE OF FIN (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	0.2	1	5	25	Necropsy BODY WT	OVERALL	F VALUE FIN	R-SQUARE FIN
Lab 2	MEAN	133	115	67	54	43	290	83	14	70%
TP=0.4	CV	27	19	41	30	29		29		
5	MEAN	155	62	58	49	37	275	73	14	69%
TP=0.4	CV	16	23	29	77	53		32		
6	MEAN	117	73	57	53	30	315	66	11	64%
TP=0.4	CV	24	22	47	27	45		31		
9	MEAN	122	79	73	59	45	332	76	29	82.00%
TP=0.4	CV	20	15	16	13	19		19		
ALL LABS	MEAN	132	83	64	54	39		74		71.00%
TP=0.4	CV	23	31	33	37	38		28		

ANOVA For VP			p VALUE	R2
Chemical effect	F=	51	0.0001	61.00%
Lab Effect	F=	3.9	0.01	3.50%
Chemical*Lab	F=	1.5	ns	

Data analyzed by SAS using Proc GLM with log10 transformed data

Table 58 Seminal Vesicle EU

FINASTERIDE (oral gavage) mg/kg/d ten days

DOSE OF FIN (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	0.2	1	5	25	Necropsy BODY WT	OVERALL	F VALUE FIN	R-SQUARE FIN
Lab 2	MEAN	316	186	89	102	63	264	151	15	70%
TP=0.4	CV	34	27	65	38	81		43		
5	MEAN	576	166	138	115	98	275	222	77	93%
TP=0.4	CV	17	18	22	17	17		22		
6	MEAN	426	193	213	132	140	315	220	18	75%
TP=0.4	CV	13	30	23	21	40		23		
9	MEAN	429	275	223	172	140	332	248	60	90.00%
TP=0.4	CV	11	20	7	16	140		14		
ALL LABS	MEAN	437	205	166	131	110		210		82.00%
TP=0.4	CV	28	30	41	30	45		24		

ANOVA For SV			p VALUE	R2
Chemical effect	F=	90	0.0001	61.00%
Lab Effect	F=	29	0.0001	15.00%
Chemical*Lab	F=	3.6	0.0002	

Data analyzed by SAS using Proc GLM with log10 transformed data

Table 59 LABC EU

FINASTERIDE (oral gavage) mg/kg/d ten days

DOSE OF FIN (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	0.2	1	5	25	Necropsy BODY WT	OVERALL	F VALUE FIN	R-SQUARE FIN
Lab 2	MEAN	301	286	254	254	248	290	269	3.7	37%
TP=0.4	CV	12	7	5	8	19		11		
5	MEAN	464	317	337	304	243	275	334	15	72%
TP=0.4	CV	11	13	17	19	15		15		
6	MEAN	512	456	542	409	473	315	478	5.5	47%
TP=0.4	CV	14	12	9	13	7		11		
9	MEAN	386	363	305	301	302	332	331	13	67.00%
TP=0.4	CV	9	9	8	5	8		8		
ALL LABS	MEAN	416	355	359	318	316		353		56.00%
TP=0.4	CV	23	21	33	22	32		12		

ANOVA For LABC			p VALUE	R2
Chemical effect	F=	2413	0.0001	14.70%
Lab Effect	F=	0	0.0001	60.00%
Chemical*Lab	F=	5.3	0.0001	

Data analyzed by SAS using Proc GLM with log10 transformed data

Table 60 GLANS PENIS EU

FINASTERIDE (oral gavage) mg/kg/d ten days

DOSE OF FIN (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	0.2	1	5	25	Necropsy BODY WT	OVERALL	F VALUE FIN	R-SQUARE FIN
Lab 2	MEAN	80	72.7	72.2	70	70	290	73	0.94	13%
TP=0.4	CV	8	10	12	12	23		14		
5	MEAN	84.4	72	68.3	70.9	61.5	275	72	11	69%
TP=0.4	CV	7	7	7	8	9		7		
6	MEAN	97.4	90.2	101	85.1	100	315	95	4.6	42%
TP=0.4	CV	9	10	11	4	4		8		
9	MEAN	107	92.5	90.9	84.8	82.1	332	91	6.3	50.00%
TP=0.4	CV	16	7	6	5	8		10		
ALL LABS	MEAN	92	81.8	83	78.2	80.7		83		44.00%
TP=0.4	CV	16	14	19	12	21		10		

ANOVA For GP			p VALUE	R2
Chemical effect	F=	10	0.0001	12.00%
Lab Effect	F=	53	0.0001	49.00%
Chemical*Lab	F=	1.9	0.04	

Data analyzed by SAS using Proc GLM with log10 transformed data

Table 61 COWPER'S GLANDS EU | FINASTERIDE (oral gavage) mg/kg/d ten days

DOSE OF FIN (oral) IN MG PER KG BODY WEIGHT PER DAY FOR 10 DAYS		0	0.2	1	5	25	Necropsy BODY WT	OVERALL	F VALUE FIN	R-SQUARE FIN
Lab 2	MEAN	28.8	24.4	15.8	14.7	10.3	290	19	5	44%
TP=0.4	CV	30	11	65	32	45		36		
5	MEAN	34.8	21.3	18.4	15.3	8.5	275	20	44	88%
TP=0.4	CV	14	16	14	20	28		17		
6	MEAN	26.4	22.5	26.6	16.2	15	315	21	6	49%
TP=0.4	CV	17	23	27	37	27		26		
9	MEAN	33.1	31.1	27.3	20.4	16	332	26	19	76.00%
TP=0.4	CV	13	15	14	22	22		16		
ALL LABS	MEAN	30.8	24.8	22	16.7	12.4		21		64.00%
TP=0.4	CV	21	22	37	30	38		24		

ANOVA For COWS			p VALUE	R2
Chemical effect	F=	33	0.0001	46.00%
Lab Effect	F=	10	0.0001	10.00%
Chemical*Lab	F=	2.1	0.02	

Data analyzed by SAS using Proc GLM with log10 transformed data

Table 62

CV ANTIANDROGENS

DDE	VP	SV	LAB C	GP	COWS	*AVERAGE*	RANK
lab 3	20	21	14	12	16	**16.6**	3
4	30	32	11	12	17	**20.4**	4
8	14	17	13	10	19	**14.6**	2
9	19	14	10	7	16	**13.2**	1
AVERAGE	**21**	**21**	**12**	**10.3**	**17**	**16.2**	
RANK	**4**	**4**	**2**	**1**	**3**		

VINCLOZOLIN	VP	SV	LAB C	GP	COWS	*AVERAGE*	RANK
1	21	34	14	10	22	**20.2**	3
3	24	21	16	10	15	**17.2**	1
5	31	21	13	11	23	**19.8**	2
7	22	23	14	12	47	**23.6**	4
AVERAGE	**27**	**24.8**	**14.3**	**10.8**	**26.8**	**20.2**	
RANK	**5**	**3**	**2**	**1**	**4**		

PROCYMIDONE	VP	SV	LAB C	GP	COWS	*AVERAGE*	RANK
2	27	32	17	17	34	**25.4**	4
7	29	19	21	12	28	**21.8**	3
8	14	17	10	11	21	**14.6**	2
9	13	10	8	7	8	**10.6**	1
AVERAGE	**20.8**	**19.5**	**14**	**11.8**	**22.8**	**18.1**	
RANK	**4**	**3**	**2**	**1**	**5**		

FINASTERIDE	VP	SV	LAB C	GP	COWS	*AVERAGE*	RANK
2	29	43	11	14	36	**26.6**	4
5	32	22	15	7	17	**18.6**	2
6	31	23	11	8	26	**19.8**	3
9	19	14	8	10	16	**13.4**	1
AVERAGE	**27.8**	**25.5**	**11.3**	**9.8**	**23.8**	**19.6**	
RANK	**5**	**4**	**2**	**1**	**3**		

LINURON	VP	SV	LAB C	GP	COWS	*AVERAGE*	RANK
1	19	20	14	10	19	**16.4**	1
4	20	22	12	12	16	**16.4**	1
5	19	21	12	10	22	**16.8**	2
6	35	26	10	14	23	**21.6**	4
AVERAGE	**23.3**	**22.3**	**12**	**11.5**	**20**	**17.8**	
RANK	**5**	**4**	**2**	**1**	**3**		

OVERALL	VP	SV	LAB C	GP	COWS
CV	23.9	22.6	12.7	10.8	22.1
RANK	5	4	2	1	3

Table 62
continued

CV	ANDROGENS						
METHYL TESTOSTERONE	VP	SV	LAB C	GP	COWS	*AVERAGE*	RANK
LAB 2	47	36	14	19	33	**27.8**	1
4	44	31	20	15	29	**27.8**	2
6	71	38	19	21	58	**41.4**	4
8	34	43	14	18	19	**32**	3
AVERAGE	49	37	16.8	18.2	35	32.3	
RANK	5	4	1	2	3		

TRENBOLONE	VP	SV	LAB C	GP	COWS	*AVERAGE*	RANK
7	27	46	18	9	49	**29.8**	2
3	51	43	16	13	23	**29.2**	1
1	28	46	18	28	31	**30.2**	3
AVERAGE	35.3	45	17.3	16.7	34.3	29.7	
RANK	4	5	2	1	3		

OVERALL	VP	SV	LAB C	GP	COWS
CV	42.1	41	17.1	17.5	34
RANK	5	4	1	2	3

Table 63

EU	VP	SV	LABC	GP	COWS
VIN	0.8	2.2	0.8	1.6	1.3
PRO	2.2	2.5	2.6	1.7	1.1
DDE	3	4	2.9	1	1.9
LIN	1.5	3	6.2	1.3	2.9
FIN	1.5	3.6	5.3	1.9	2.1
MT	0.9	0.8	1.6	1.4	4.1
TREN	0.54	0.47	0.54	1.9	0.86
JAPAN					
VIN	1.8	1	0.53	1.1	0.76
DDE	1.8	5	3.8	0.7	1.2
MT	1.1	2.4	0.4	0.25	0.22

F values for dose by lab interactions
yellow shaded values are sig p<0.05
blue shaded values are sig p <0.01

Phase 2 Hershberger Assay OECD Multi-laboratory Study

Sept 30, 2003

prepared by
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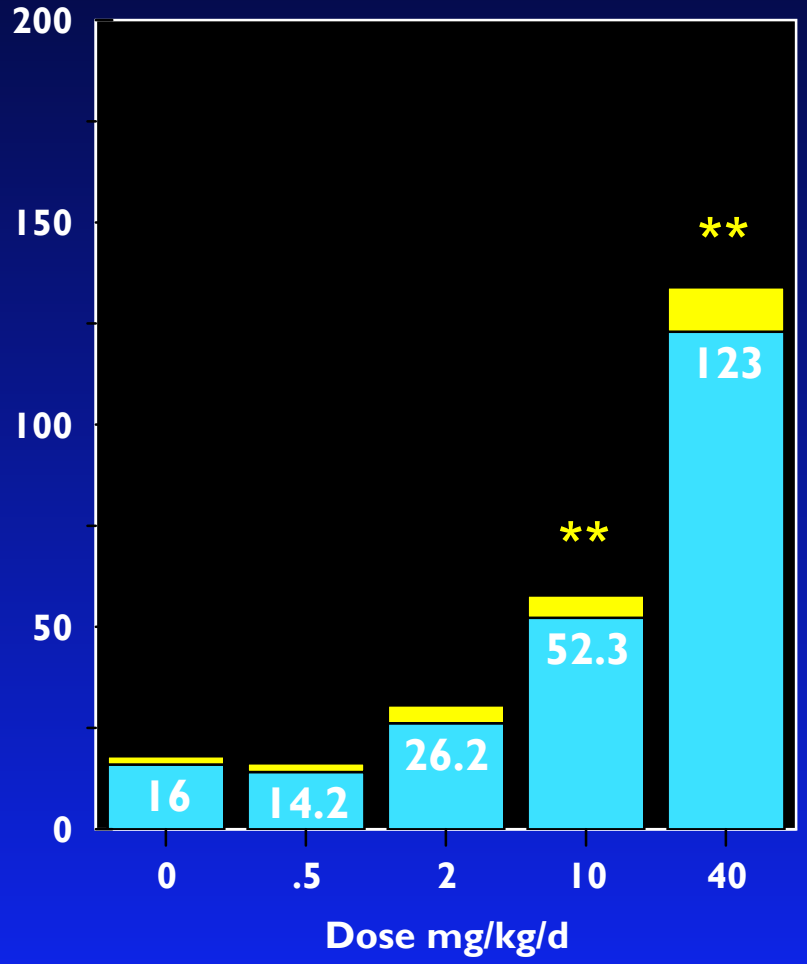
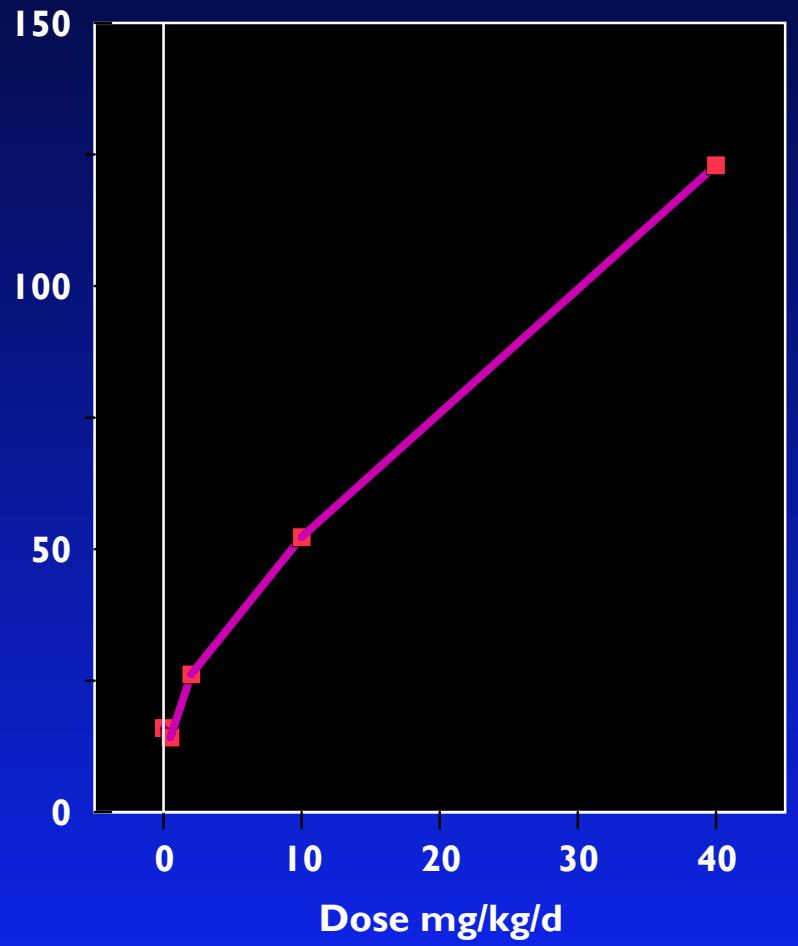
Phase 2
OECD Hershberger Assay
Interlaboratory study

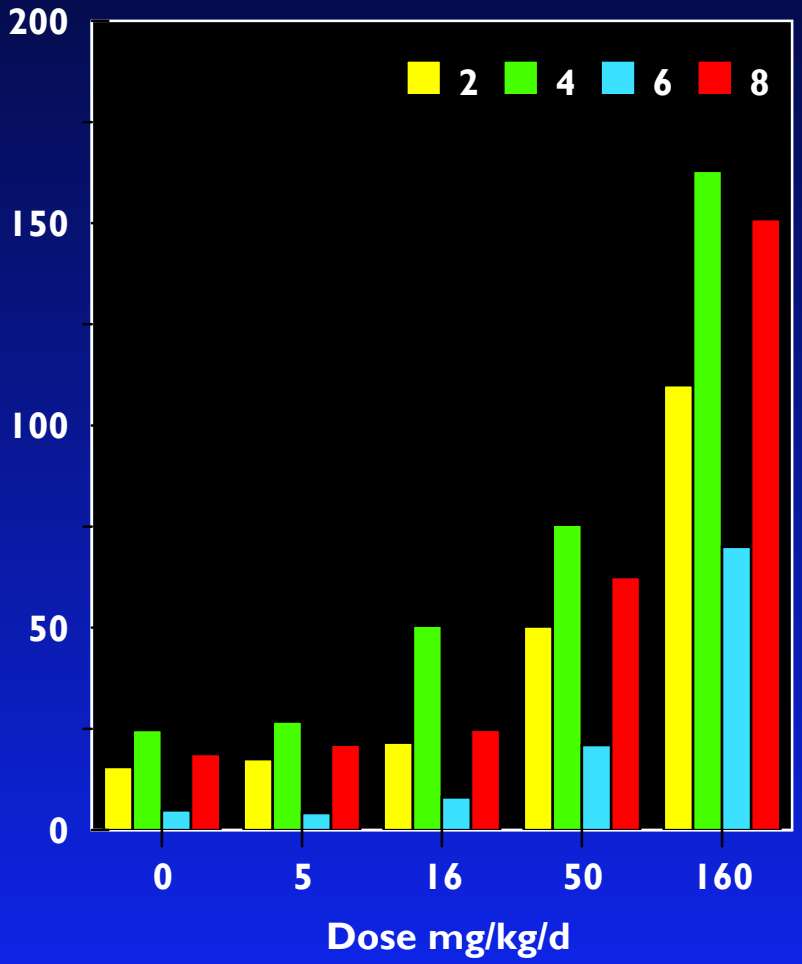
Methyltestosterone data from EUUKAS

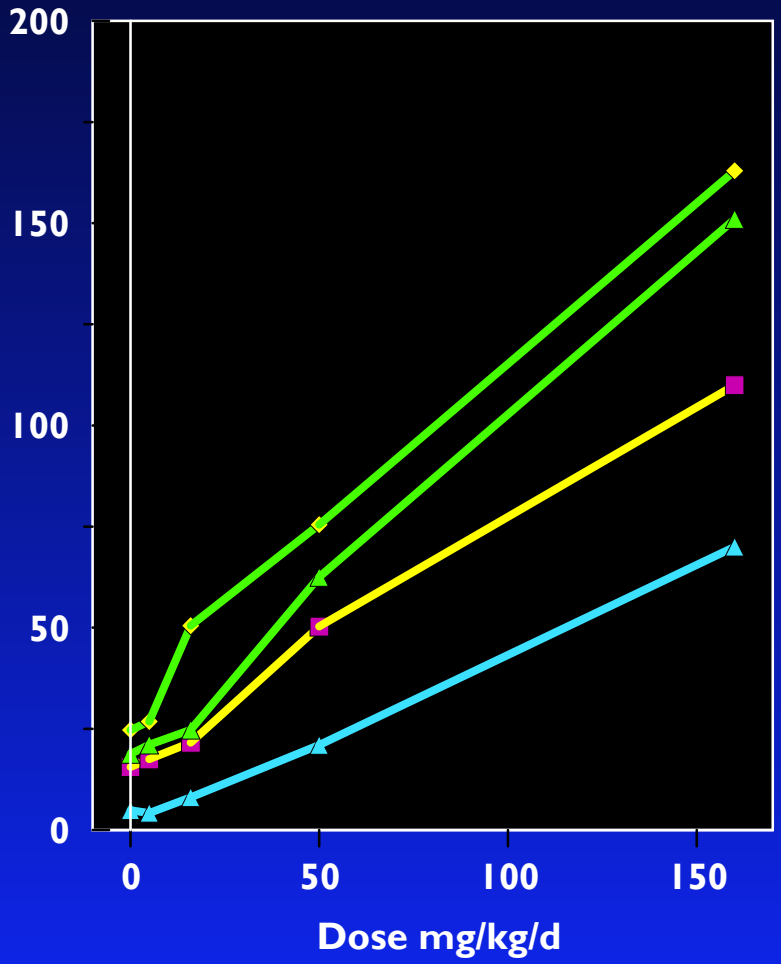
1. Effect of MT on Ventral Prostate weights. Data from four labs



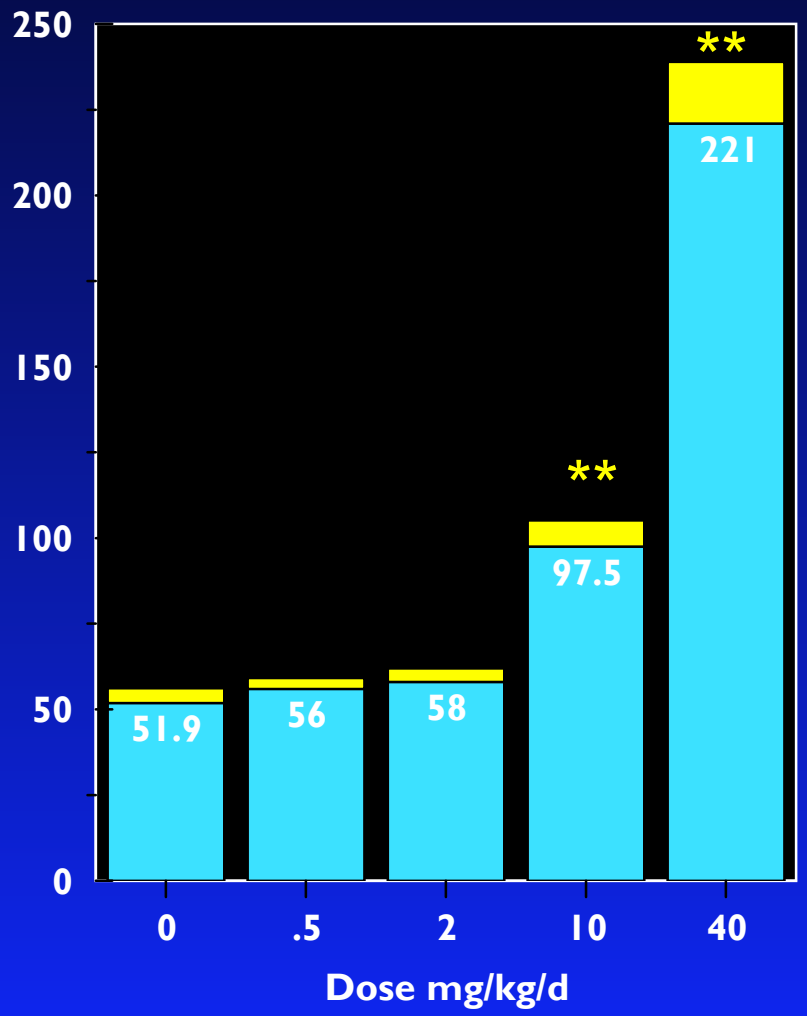


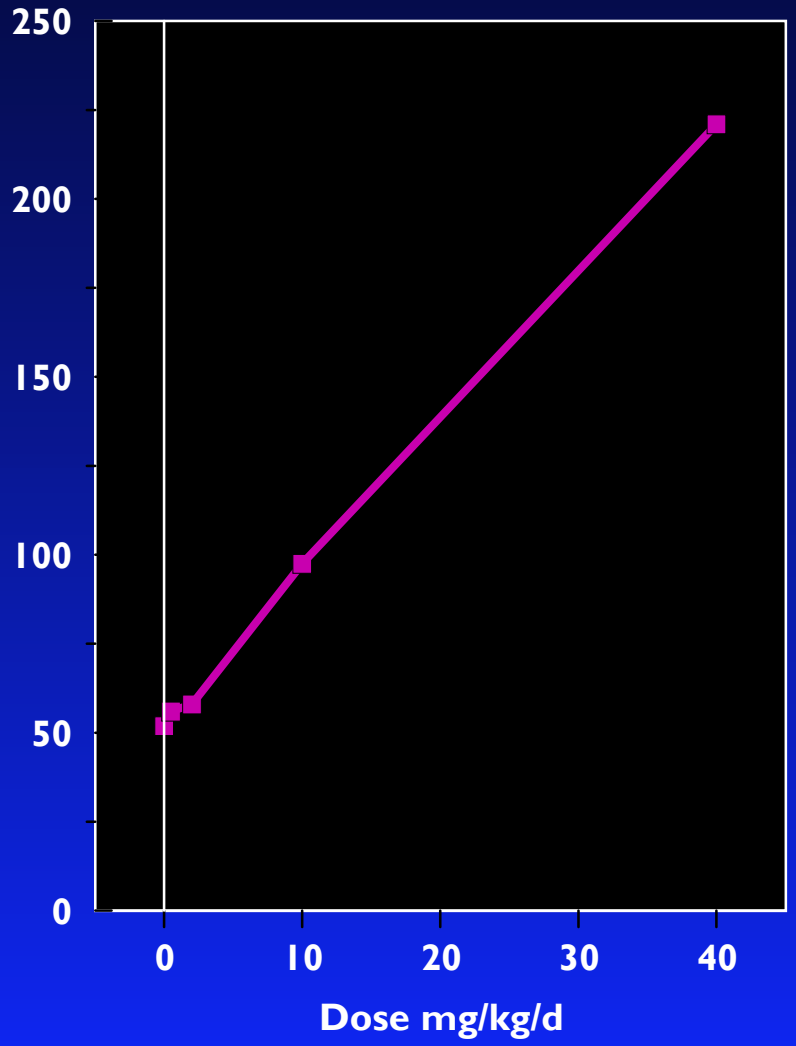
2. Effect of MT on VP weights. Data from four labs



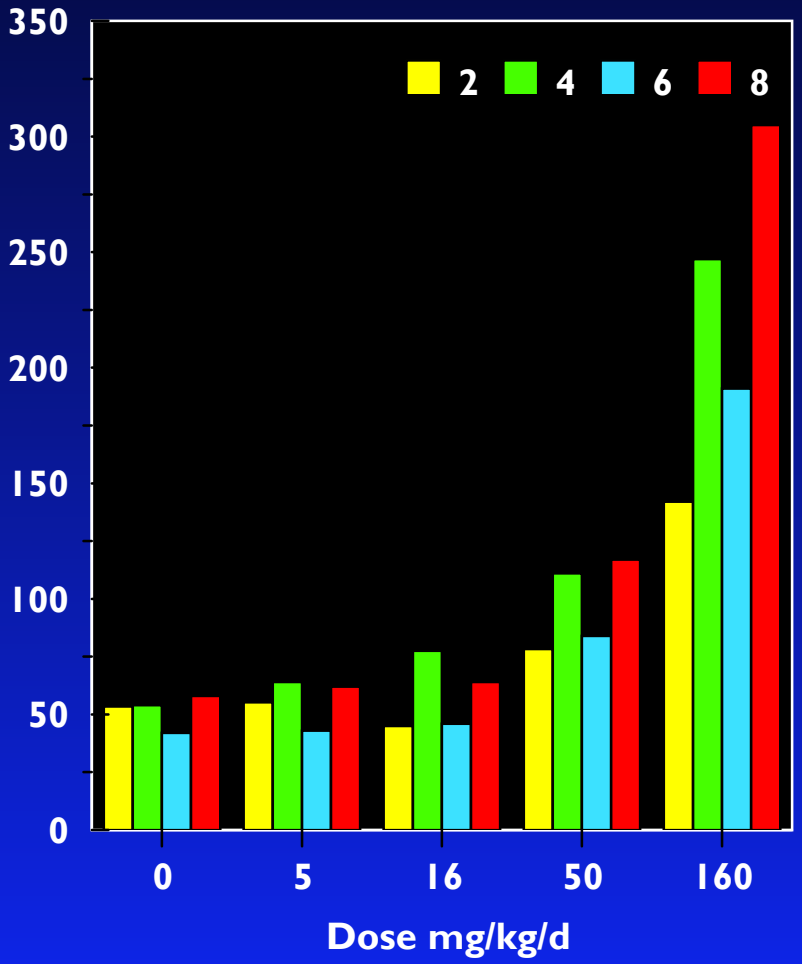


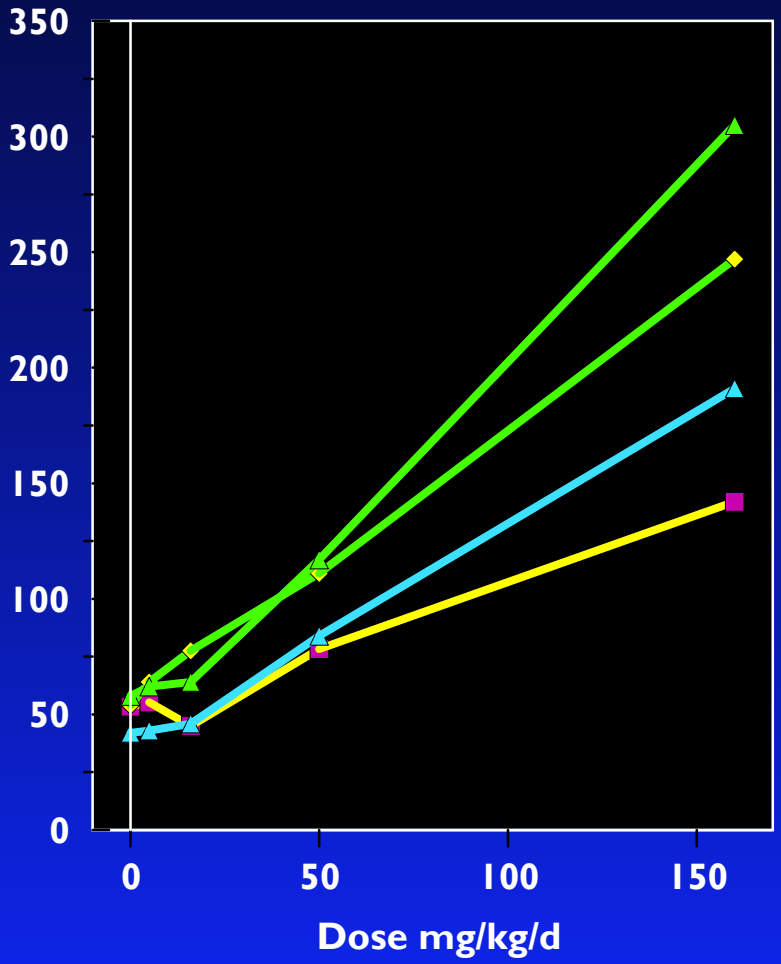
3. Effect of MT on Seminal Vesicle weights. Data from four labs



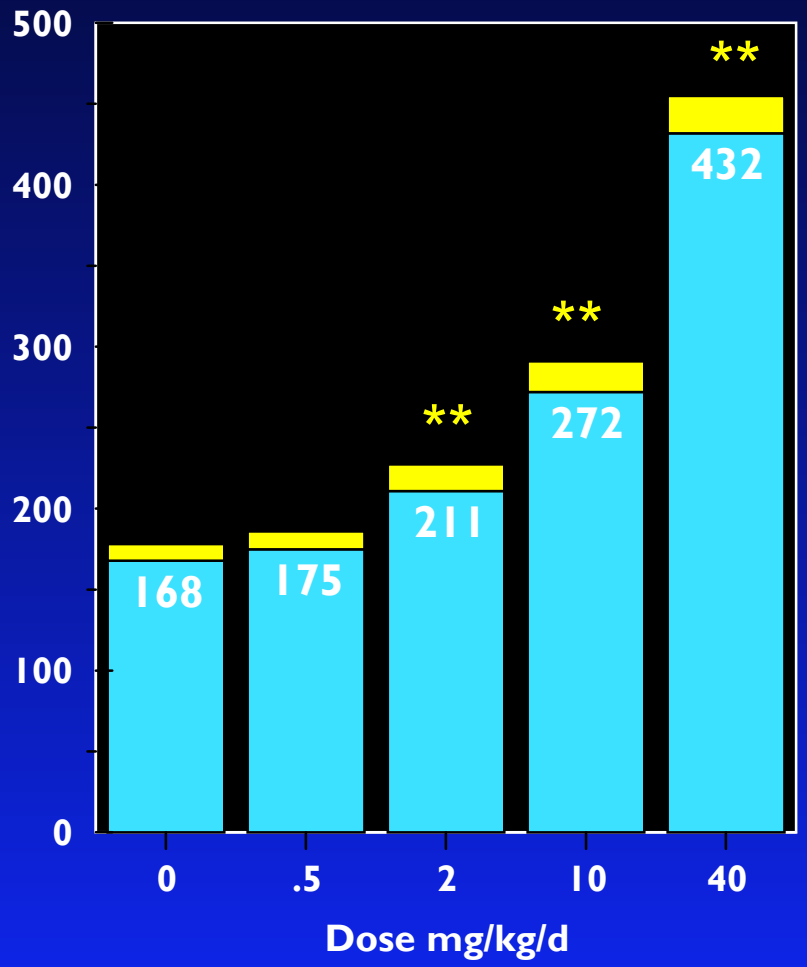


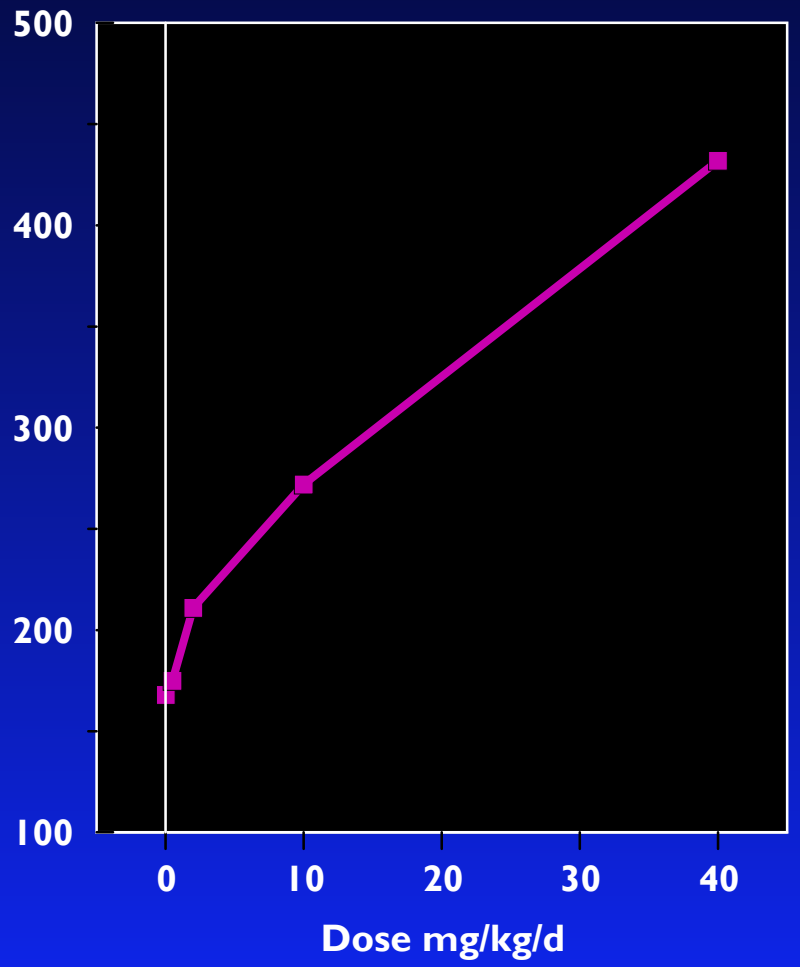
4. Effect of MT on SV weights. Data from four labs



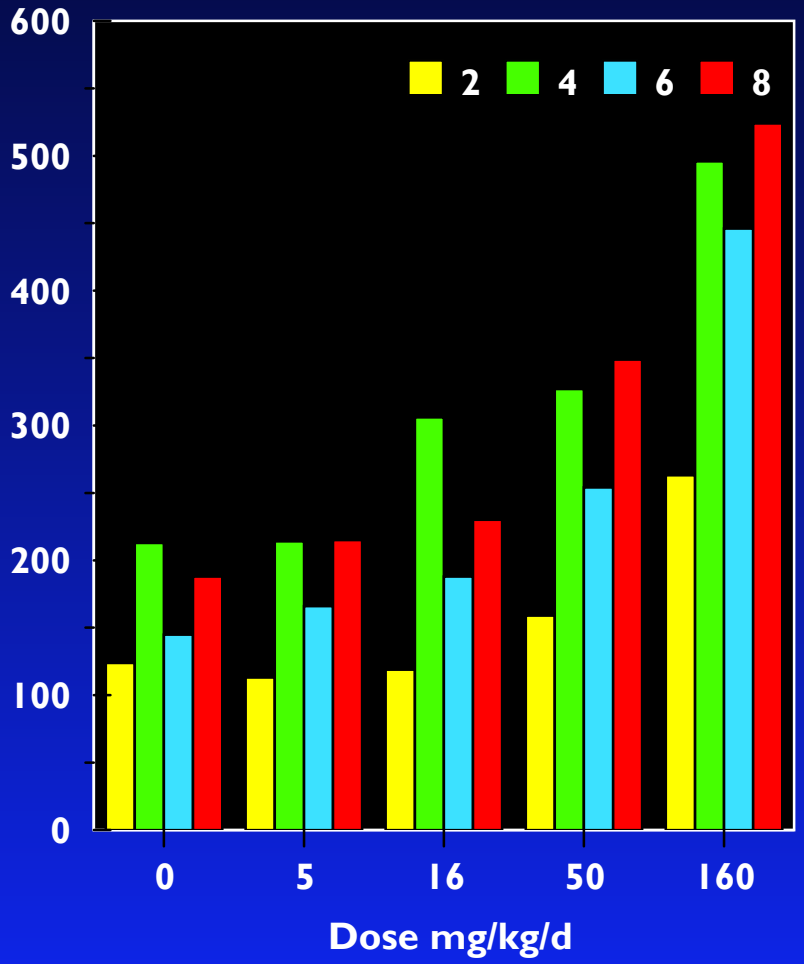


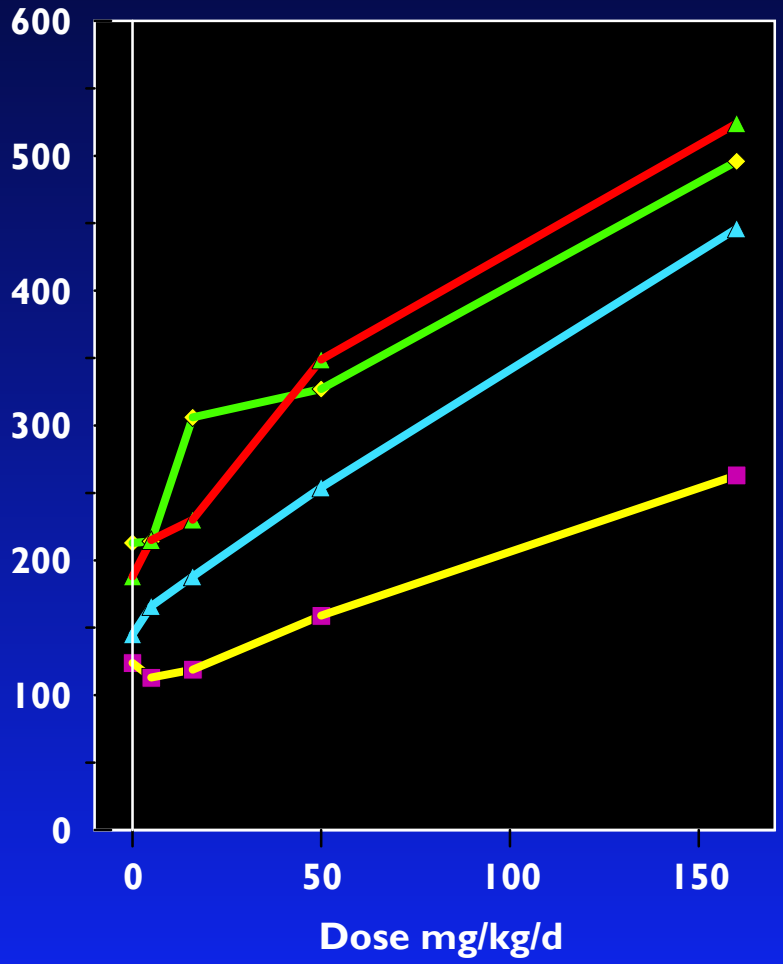
5. Effect of MT on LABC weights. Data from four labs



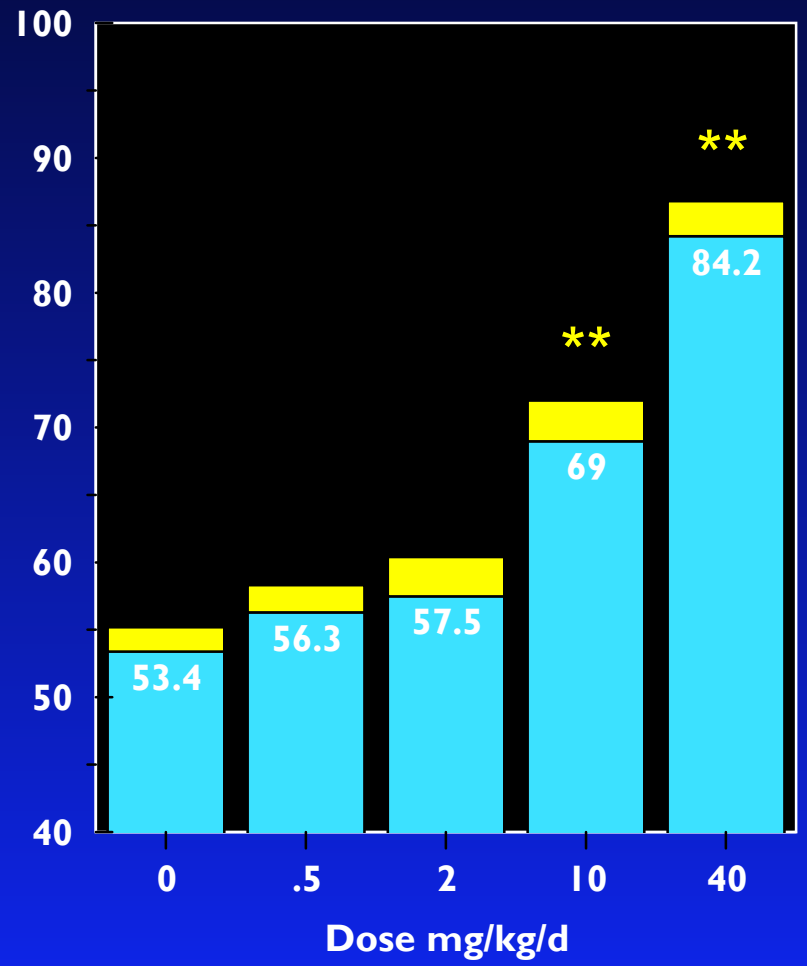


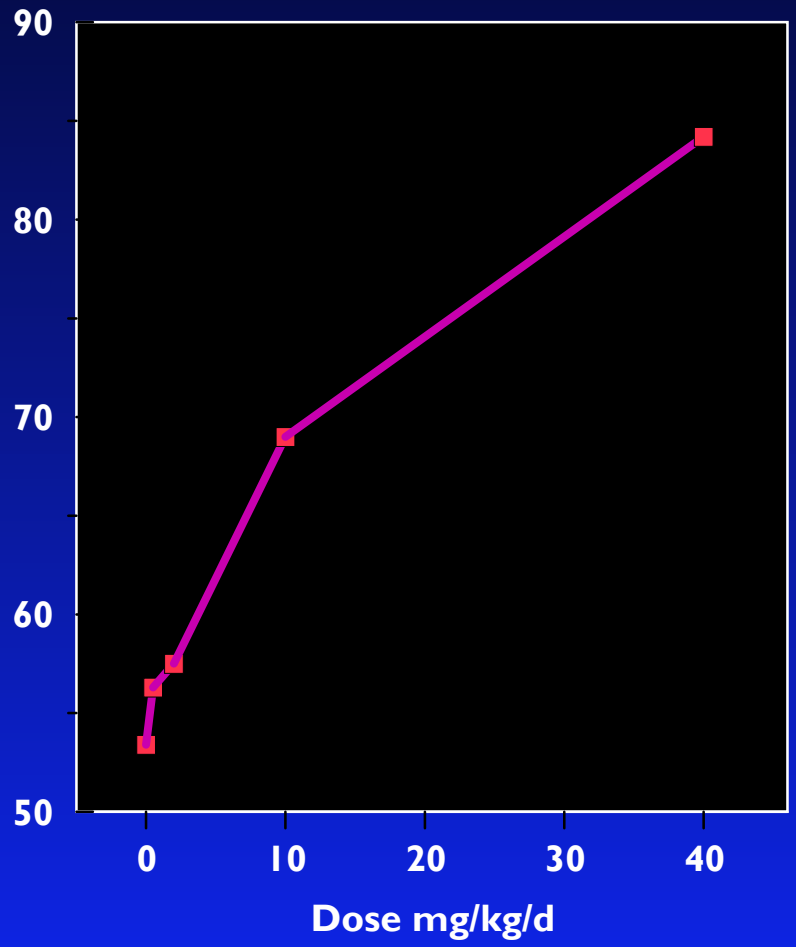
6. Effect of MT on LABC weights. Data from four labs



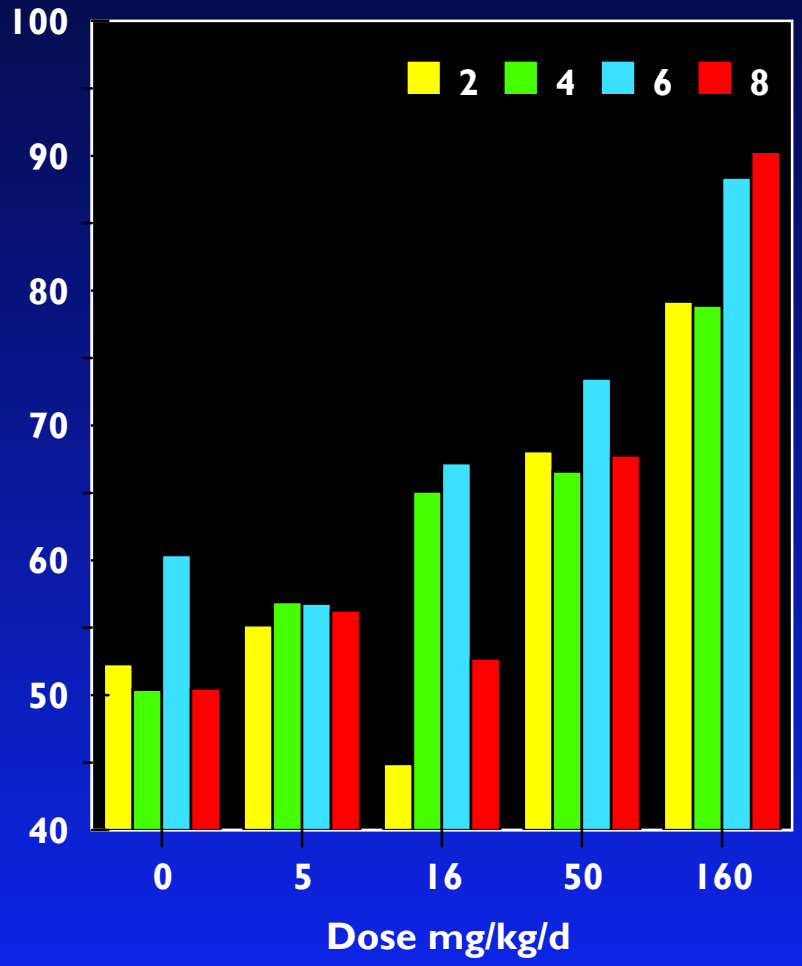


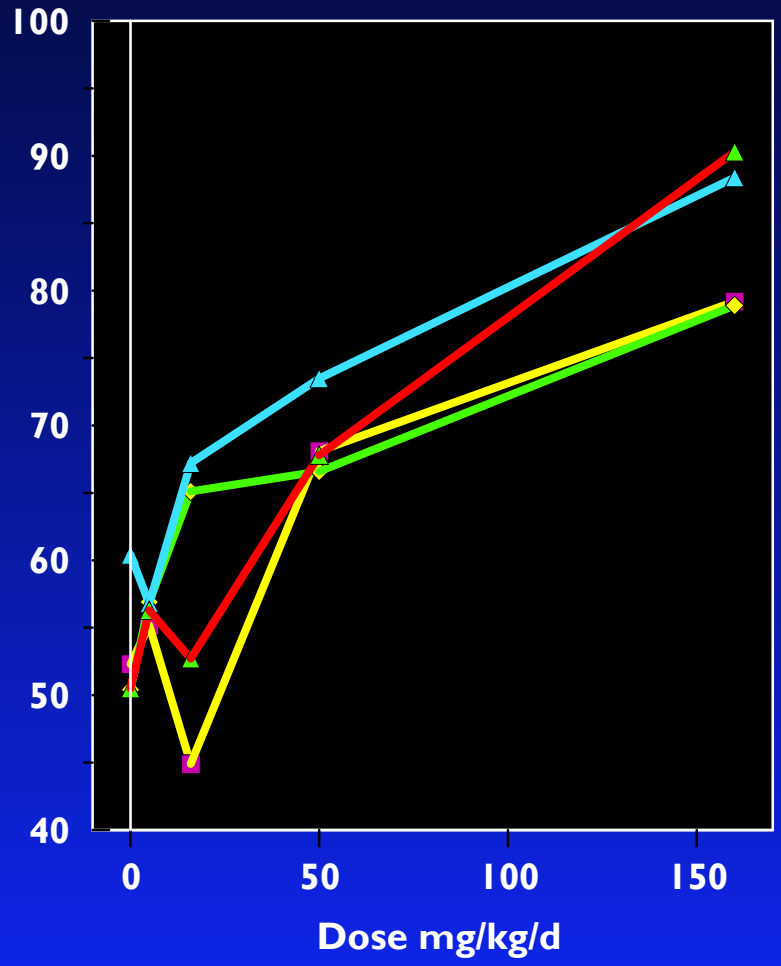
7. Effect of MT on Glans penis weights. Data from four labs



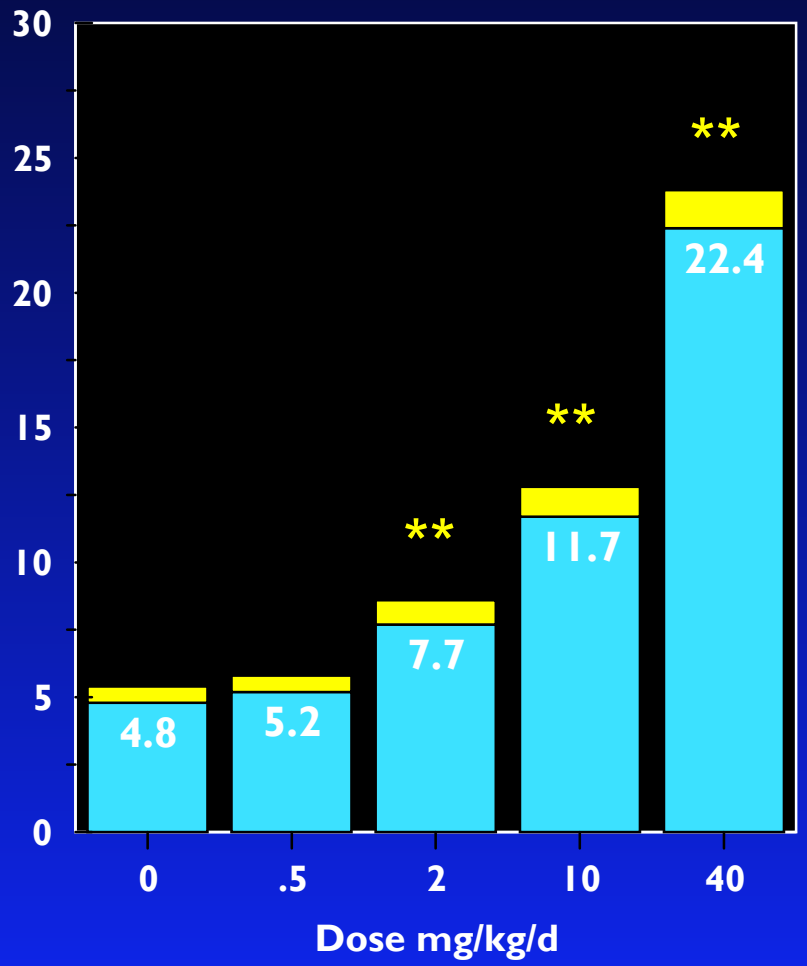


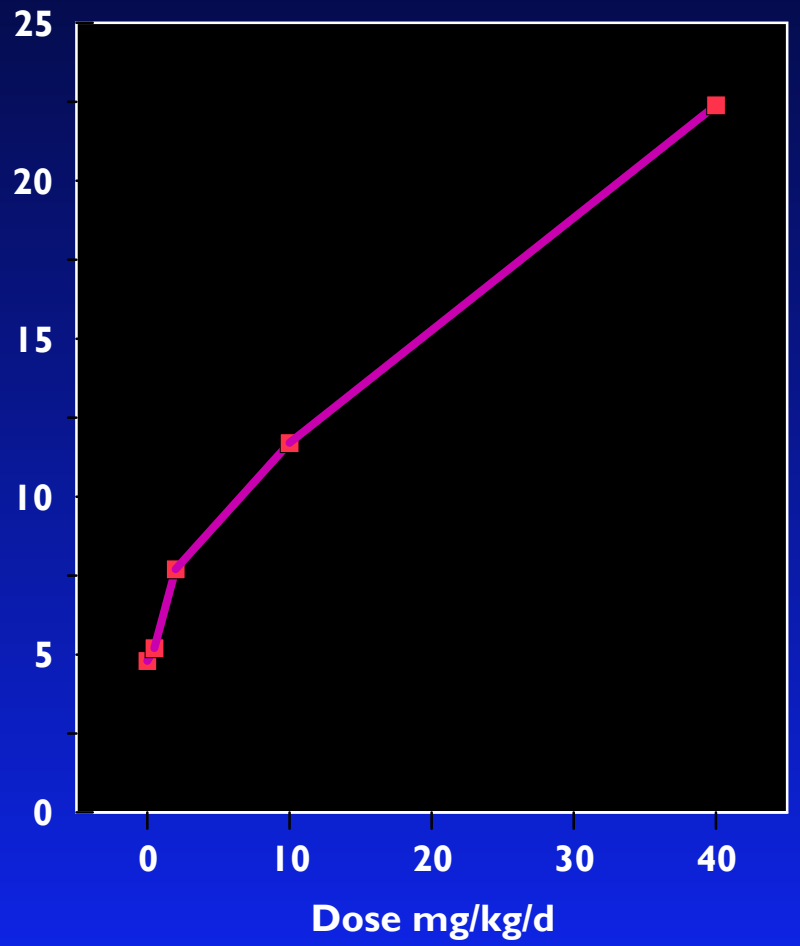
8. Effect of MT on GLANS PENIS weights. Data from four labs



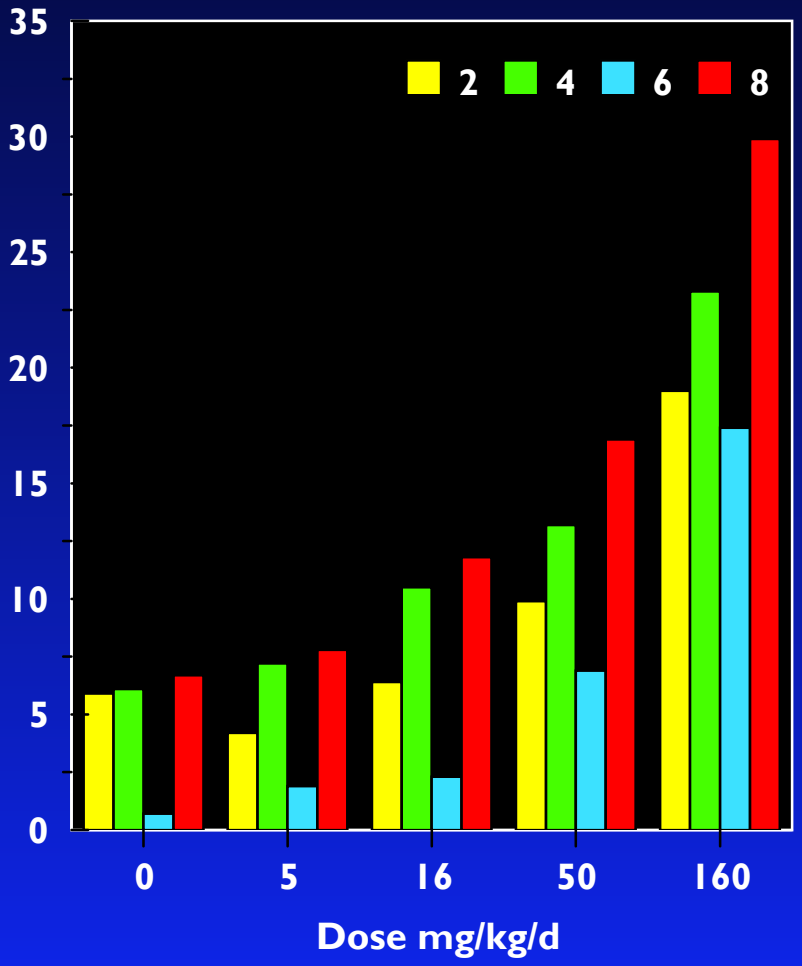


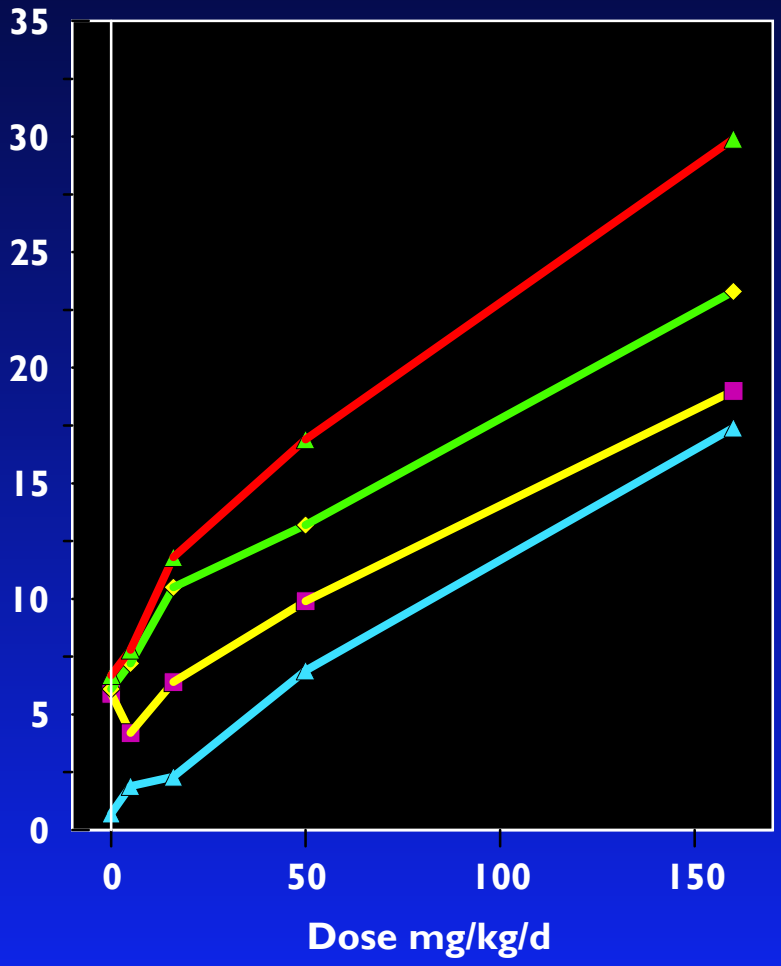
9. Effect of MT on Cowper's gland weights. Data from four labs



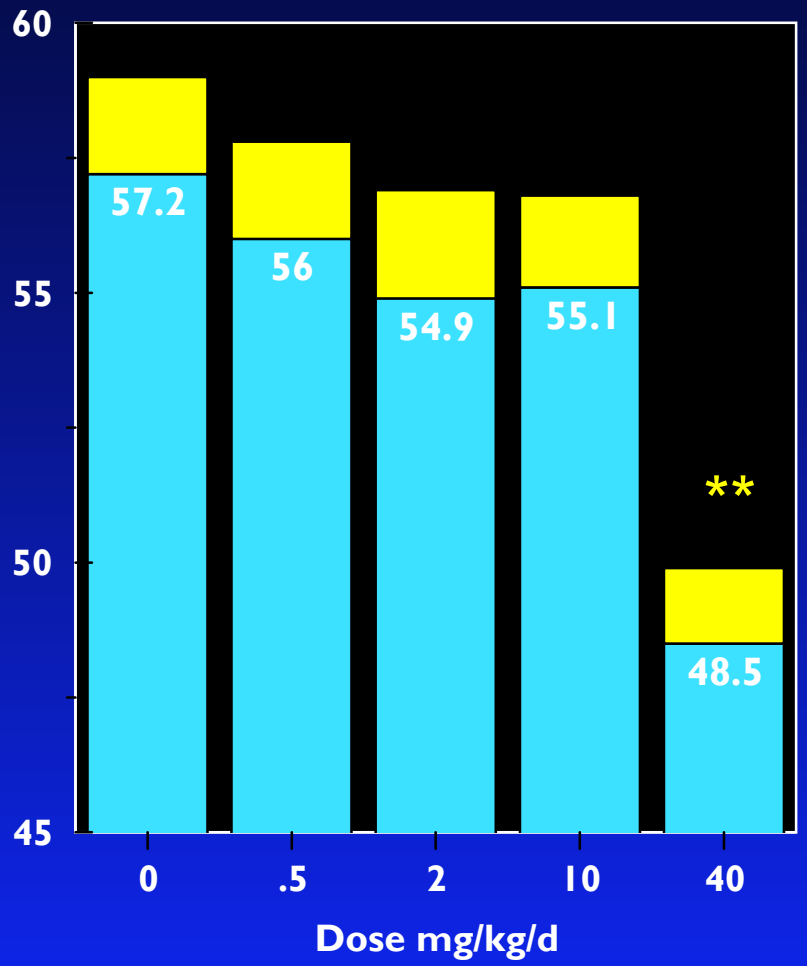


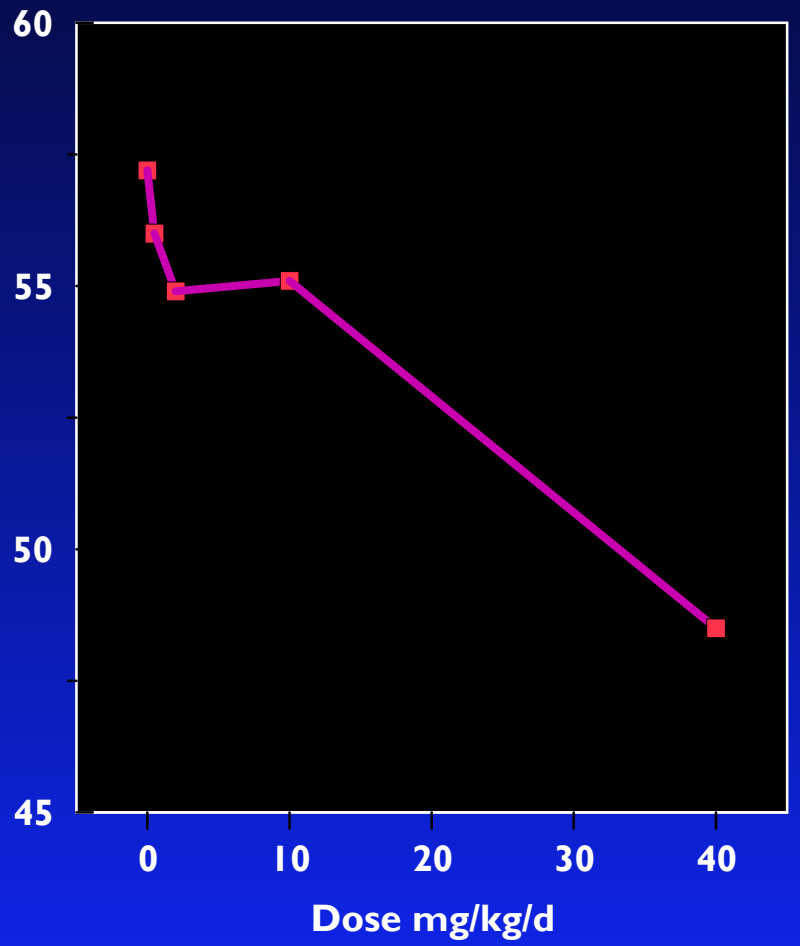
10. Effect of MT on COWPER'S GLAND weights. Data from four labs



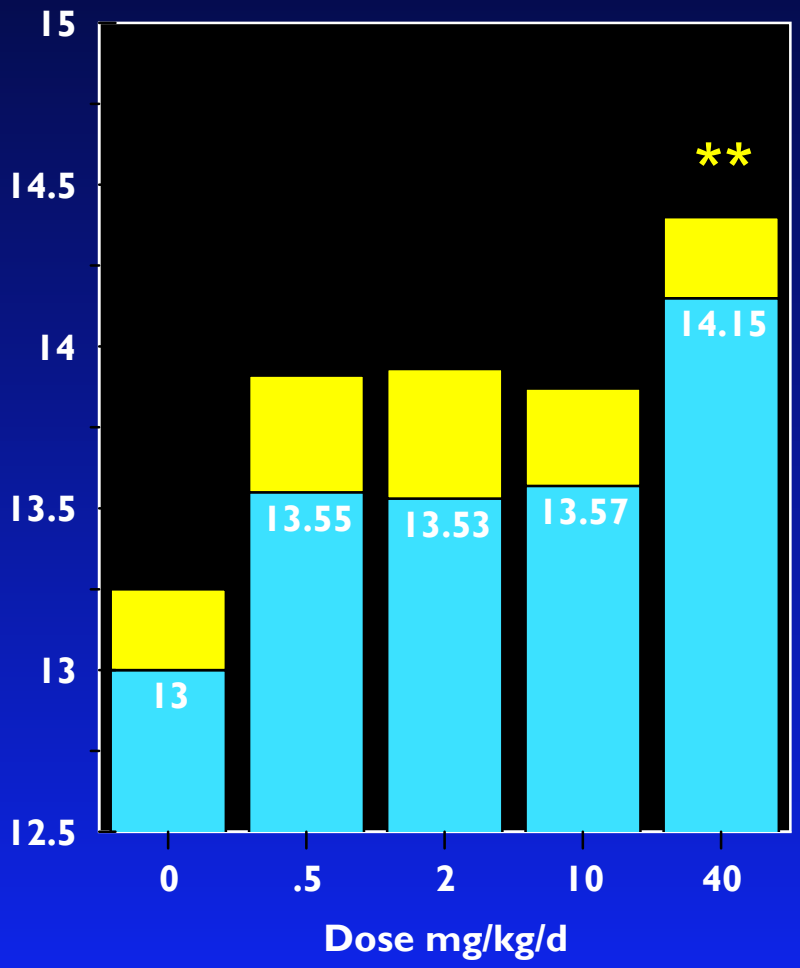


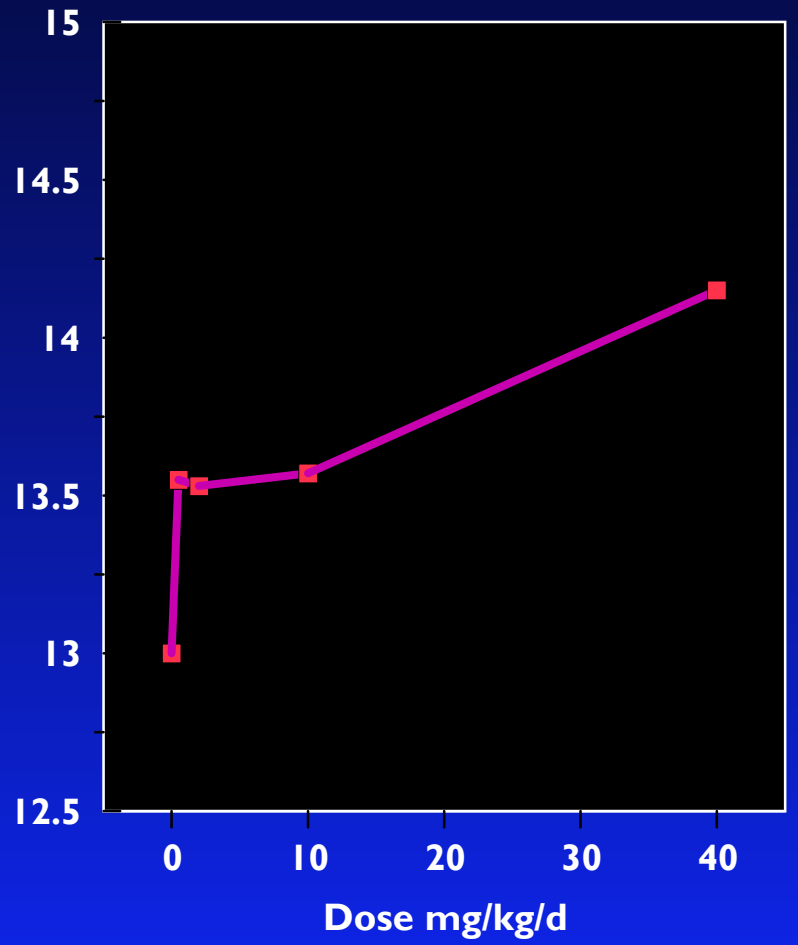
11. Effect of MT on Adrenal weights. Data from four labs



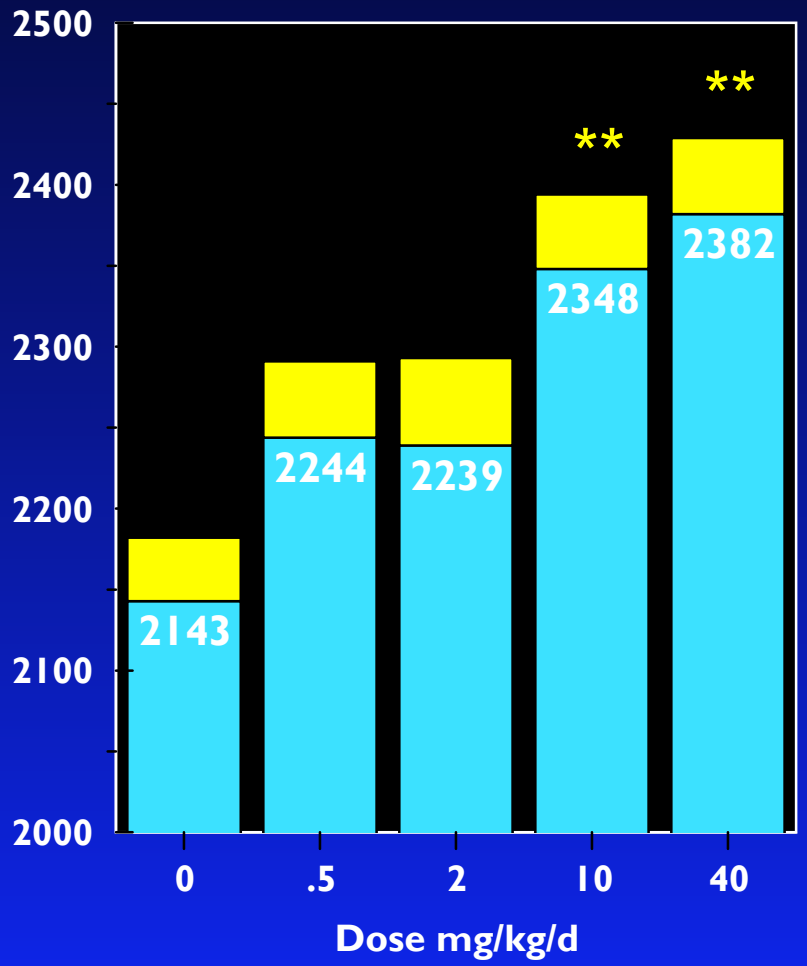


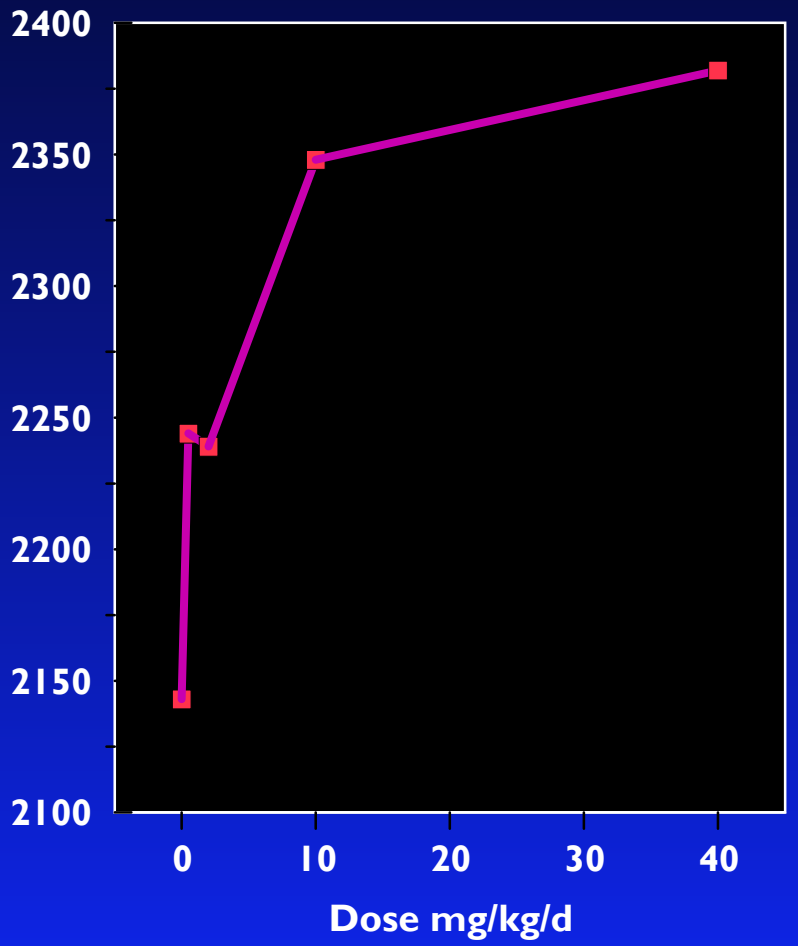
12. Effect of MT on Liver weights. Data from four labs



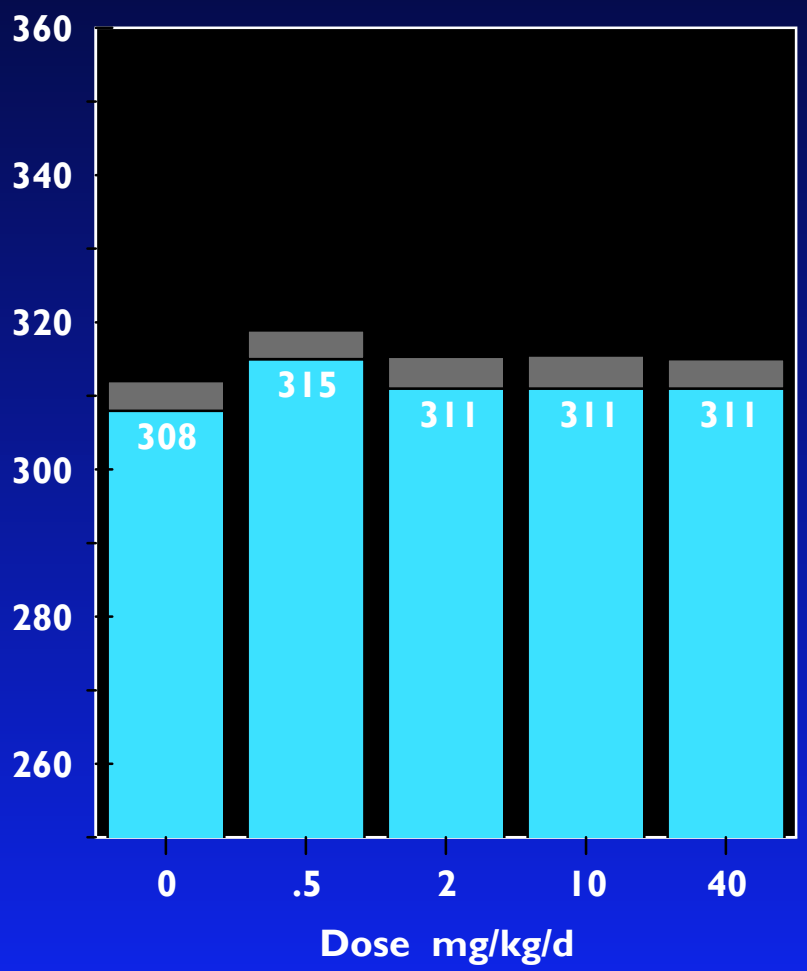


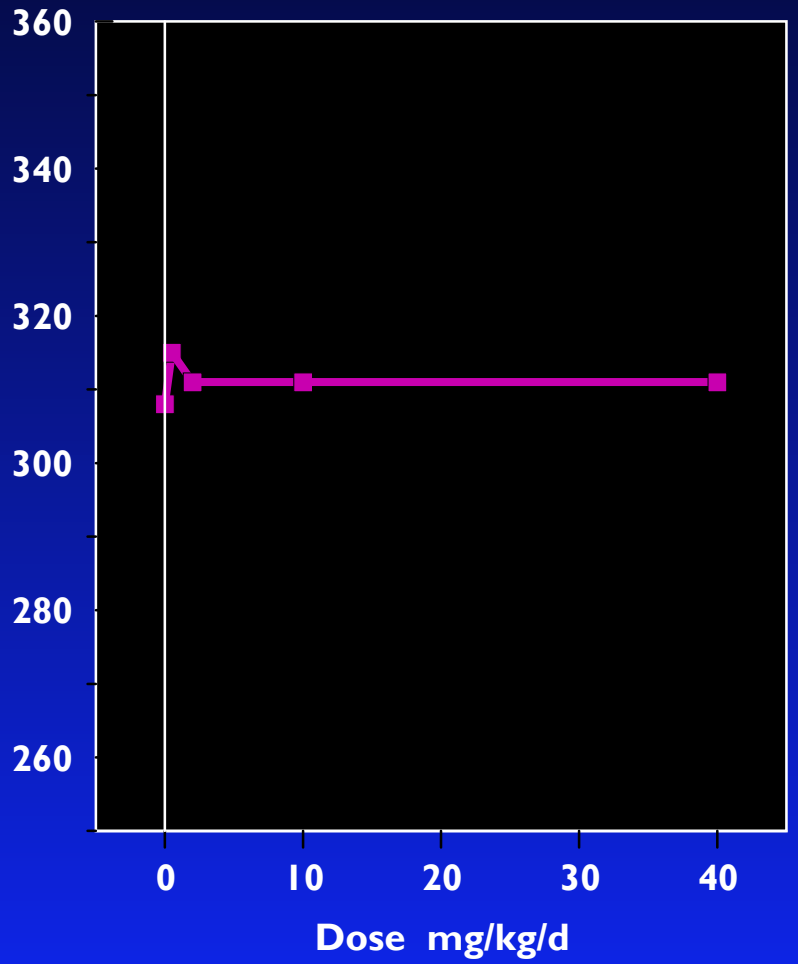
13. Effect of MT on kidney weights. Data from four labs





14. Effects of MT on Body weight at necropsy



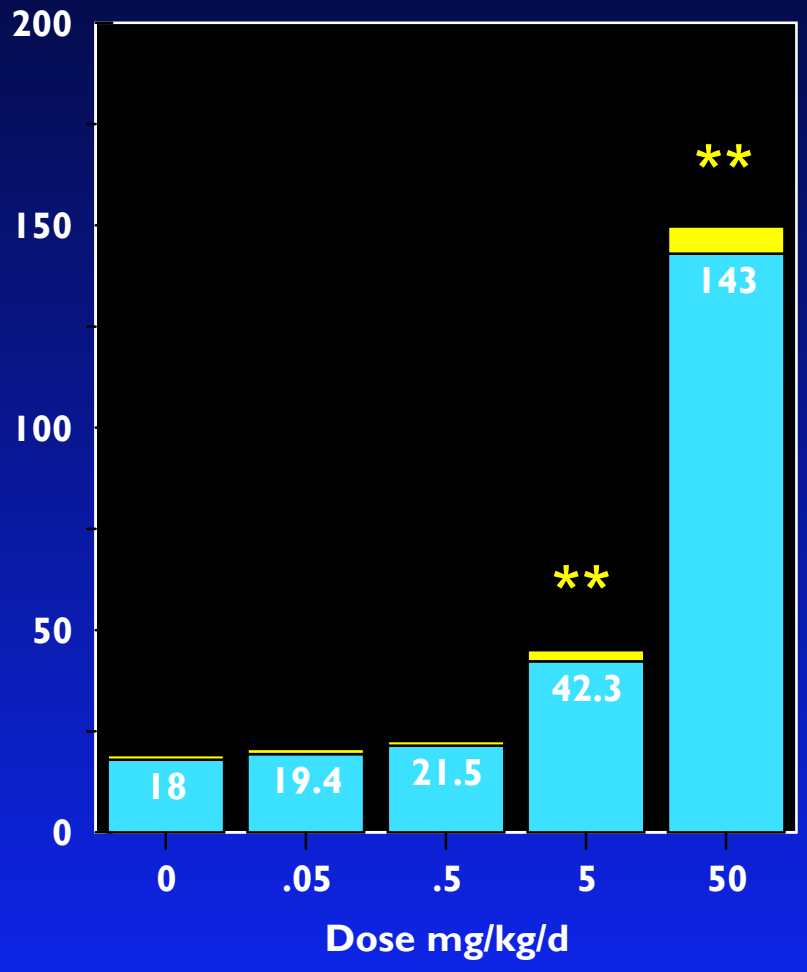


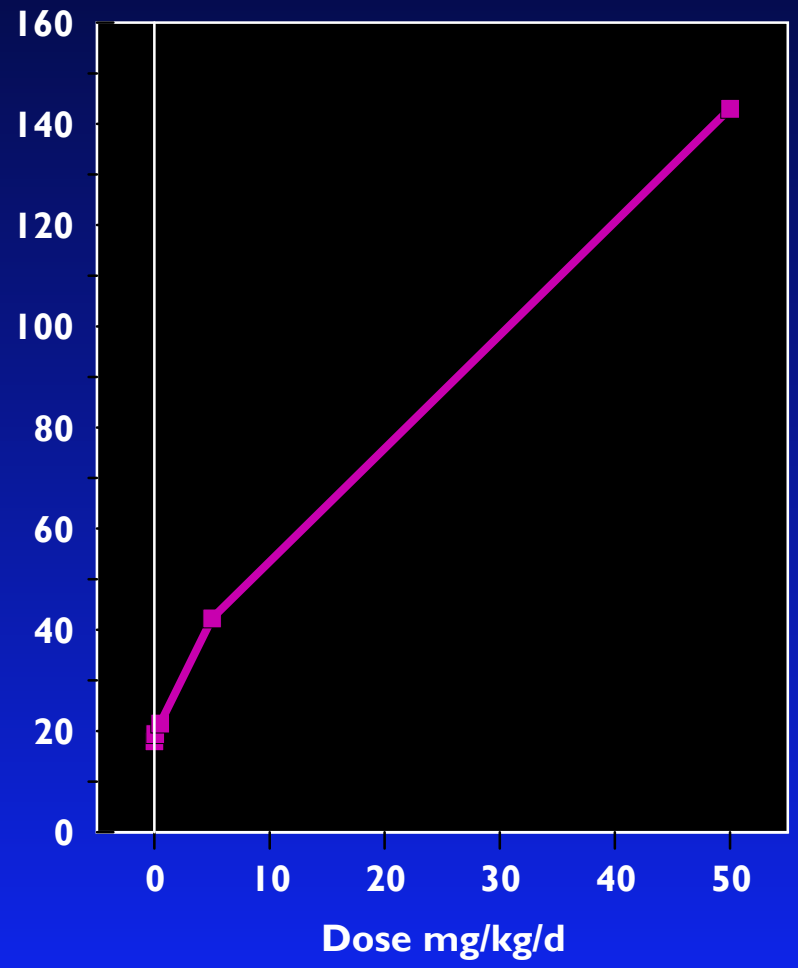
Hershberger Assay Interlaboratory study

Japanese labs using methyltestosterone

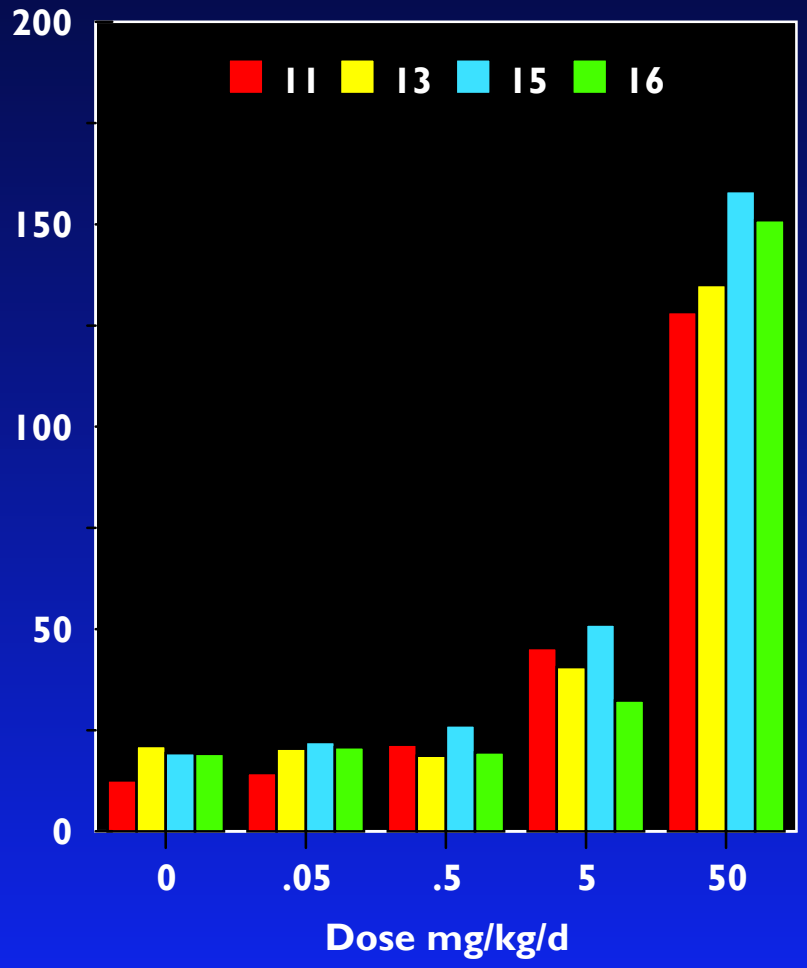
Jan 2003

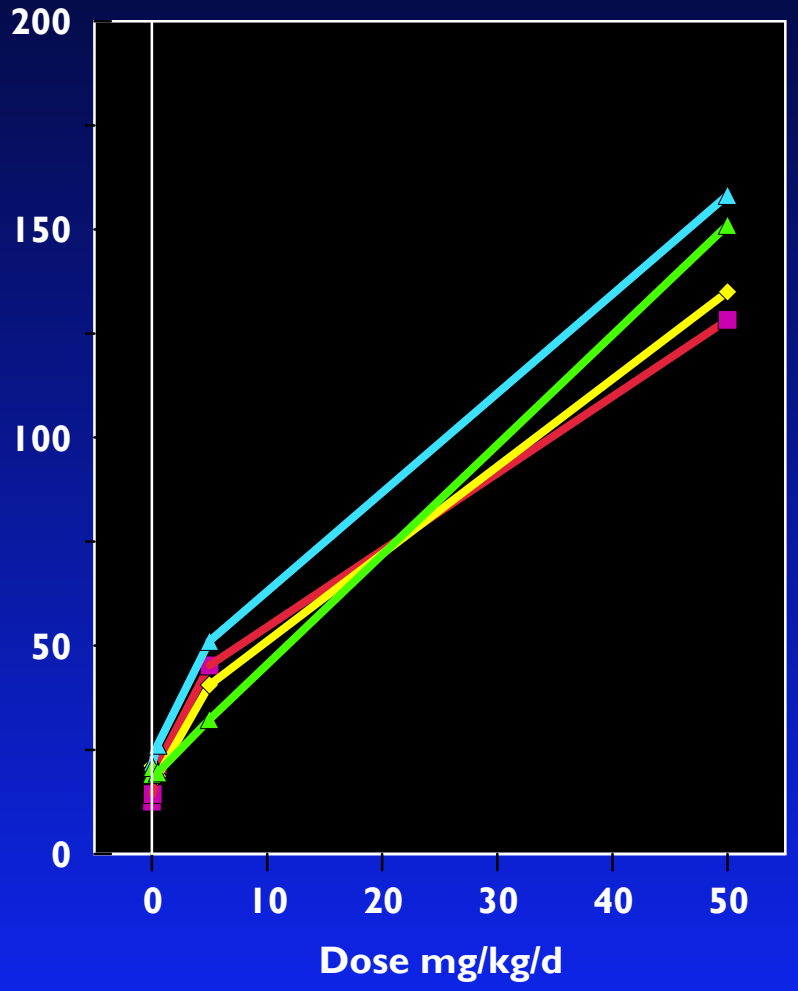
15. Effect of MT on ventral prostate weights. Data from four labs



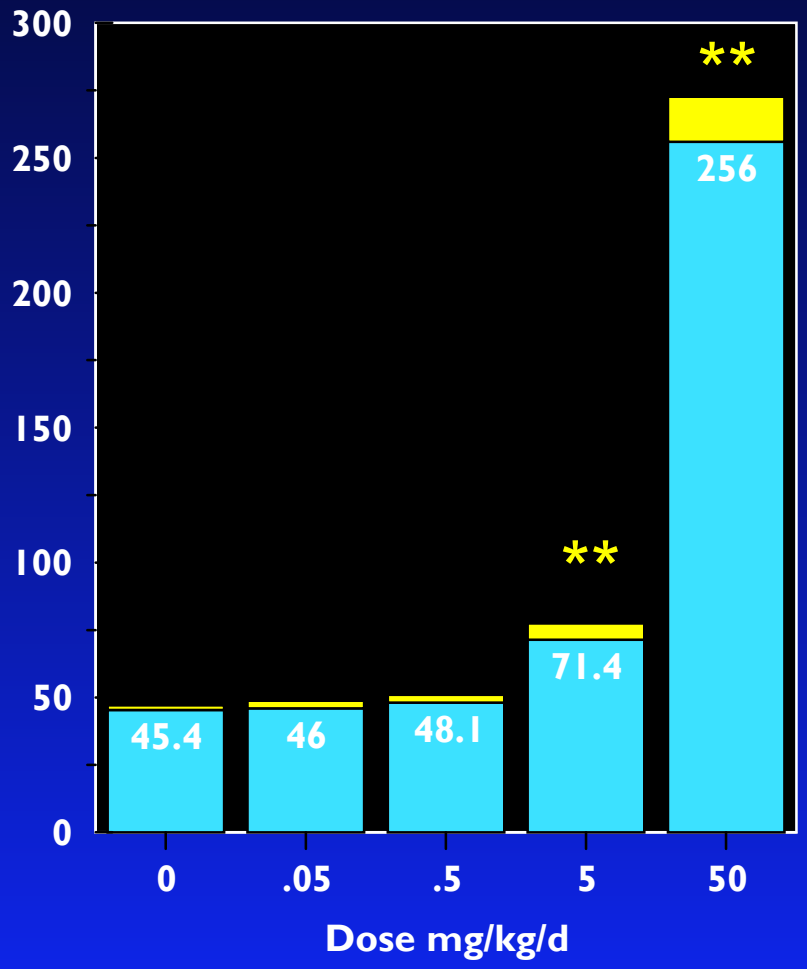


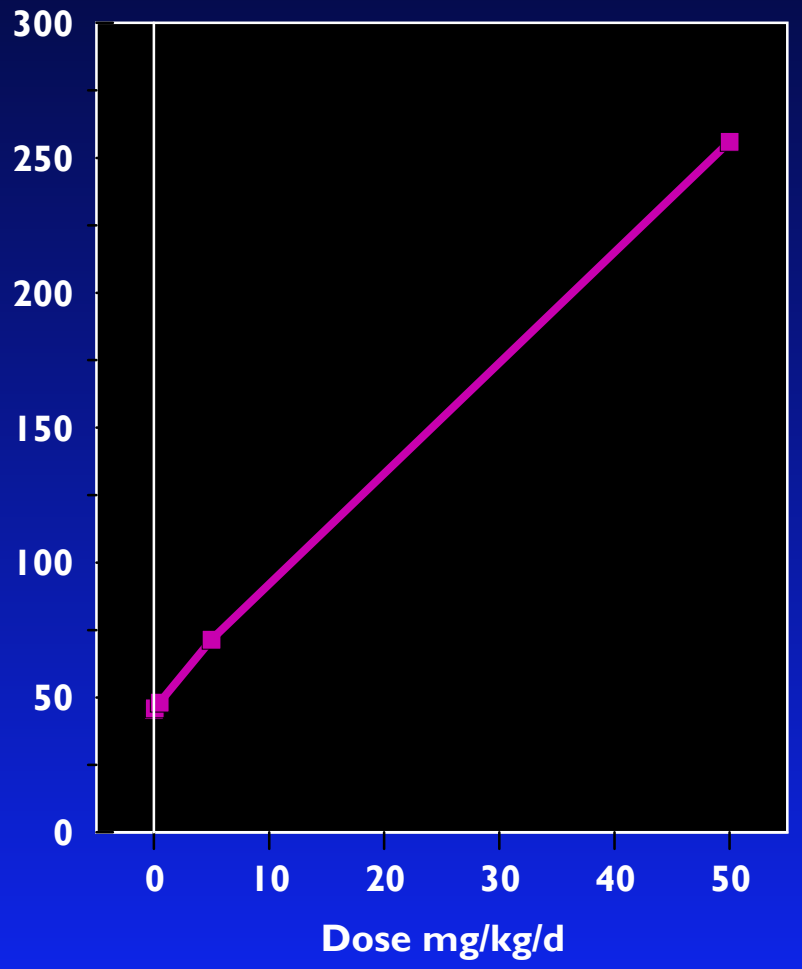
16. Effect of MT on ventral prostate weights. Data from four labs



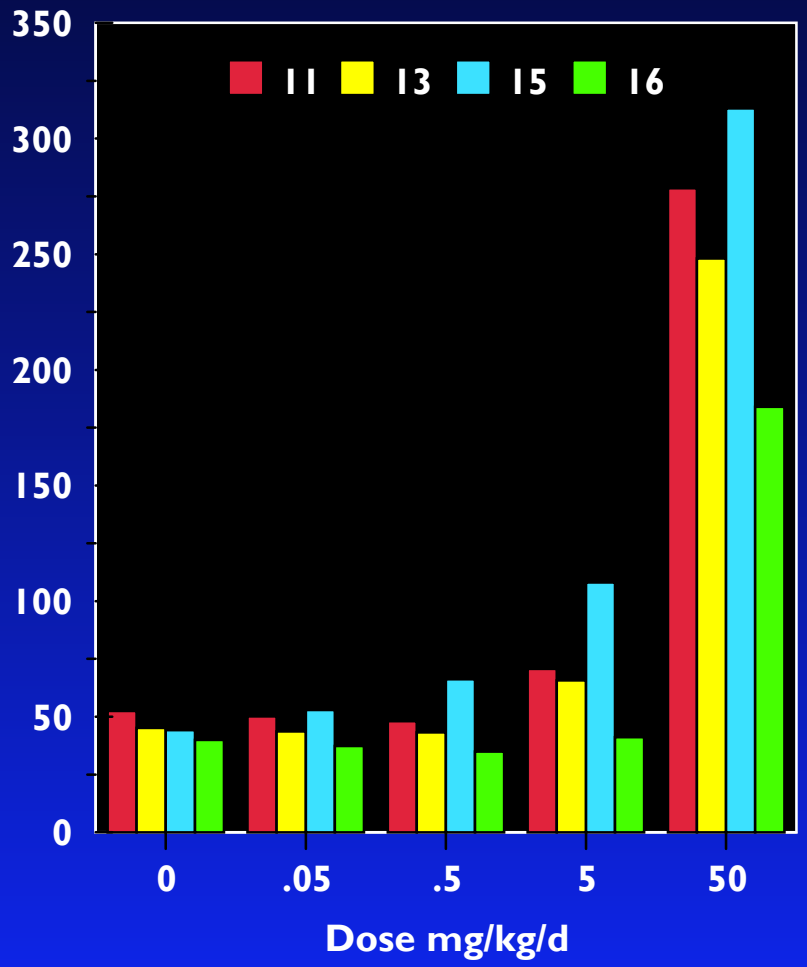


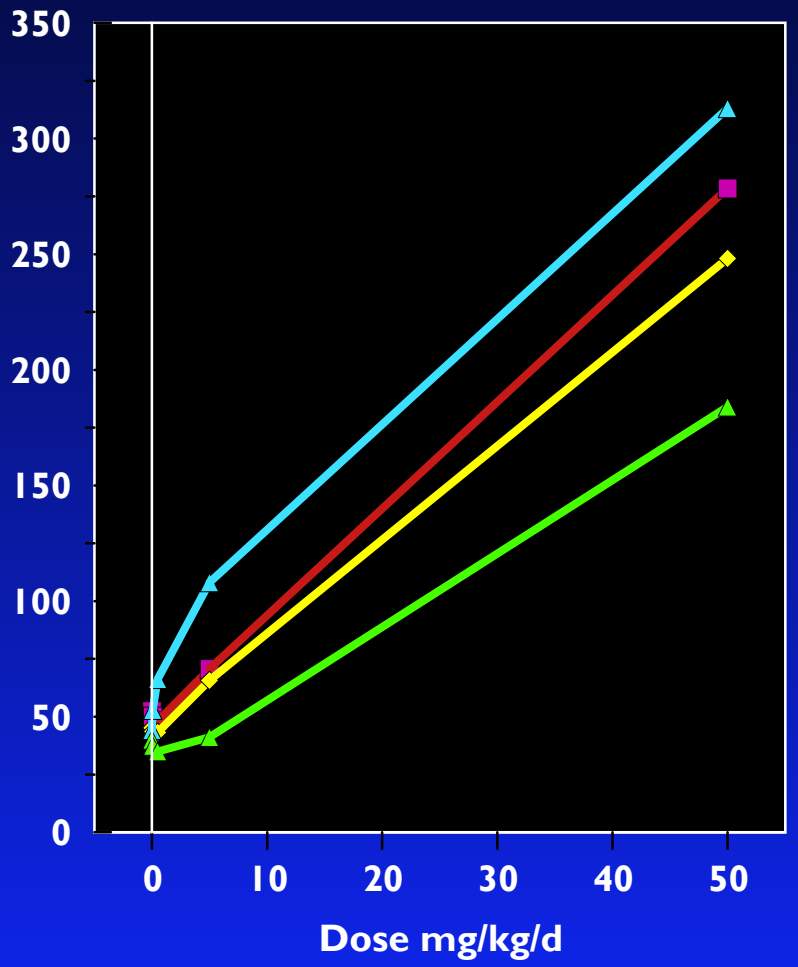
17. Effect of MT on seminal vesicle weights. Data from four labs



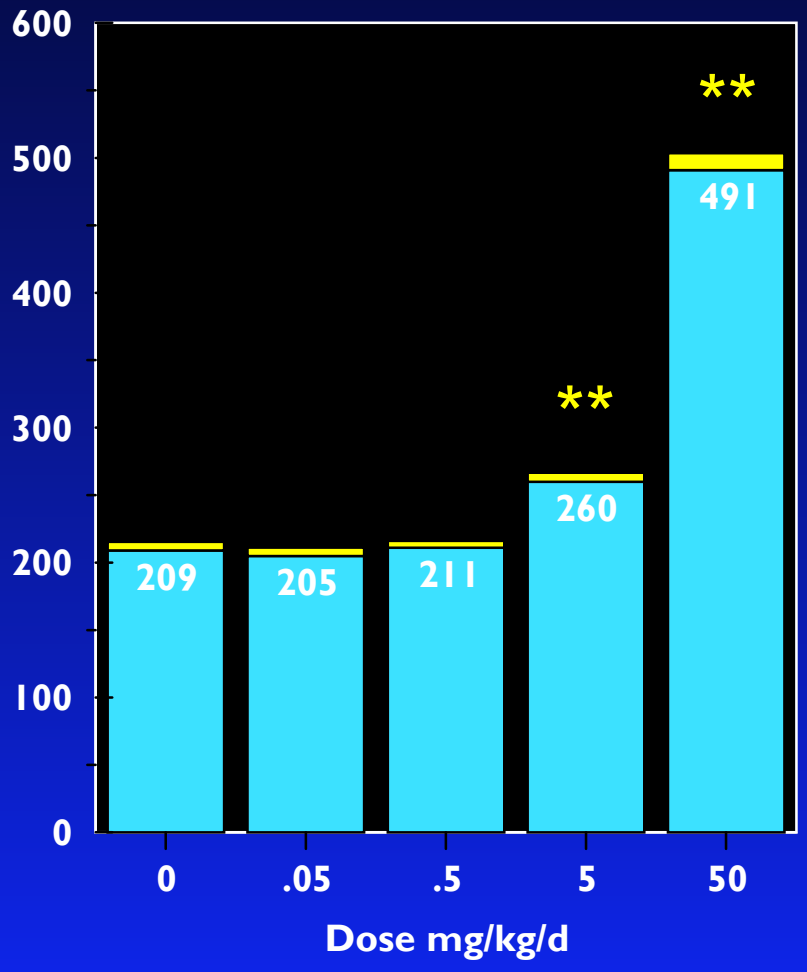


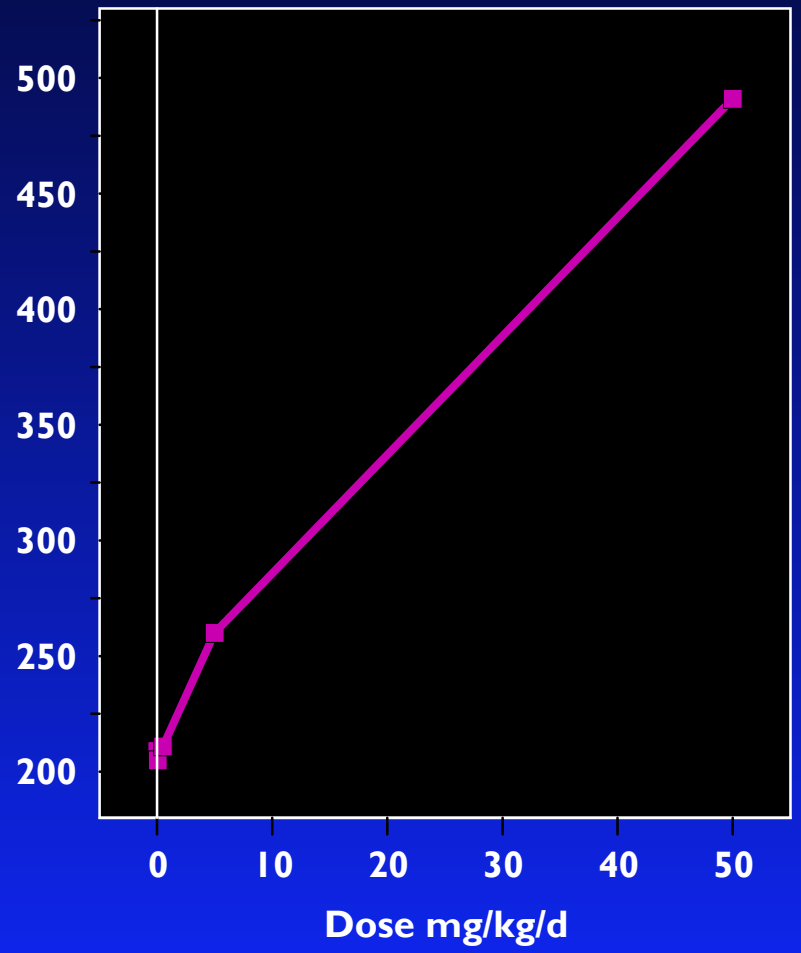
18. Effect of MT on seminal vesicle weights. Data from four labs



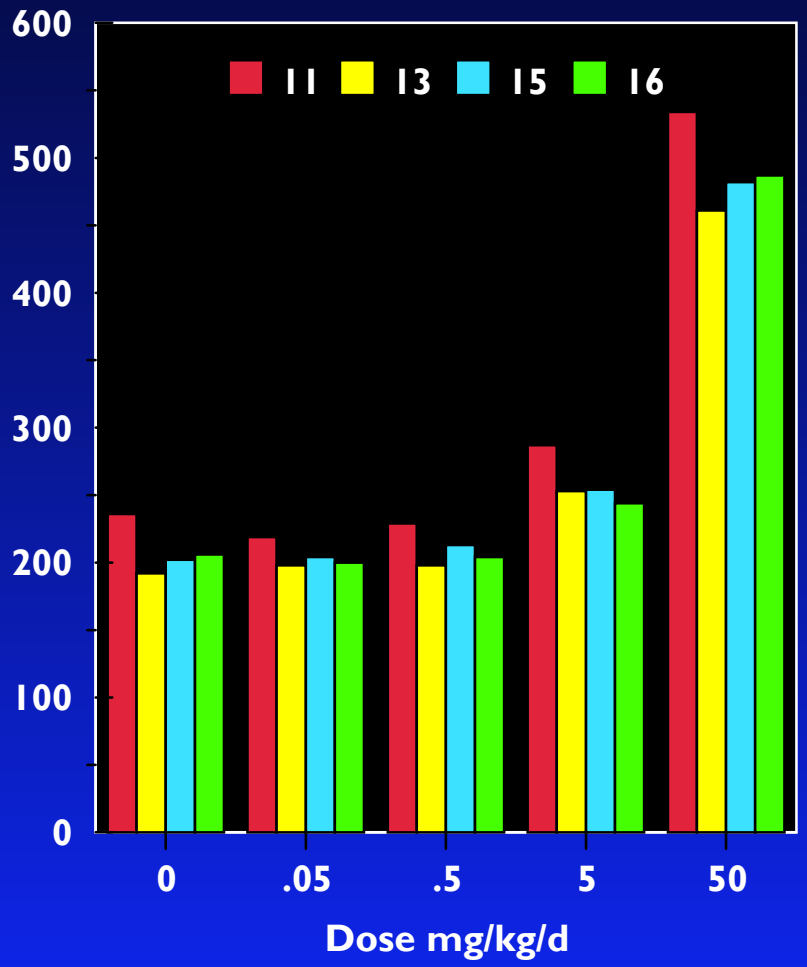


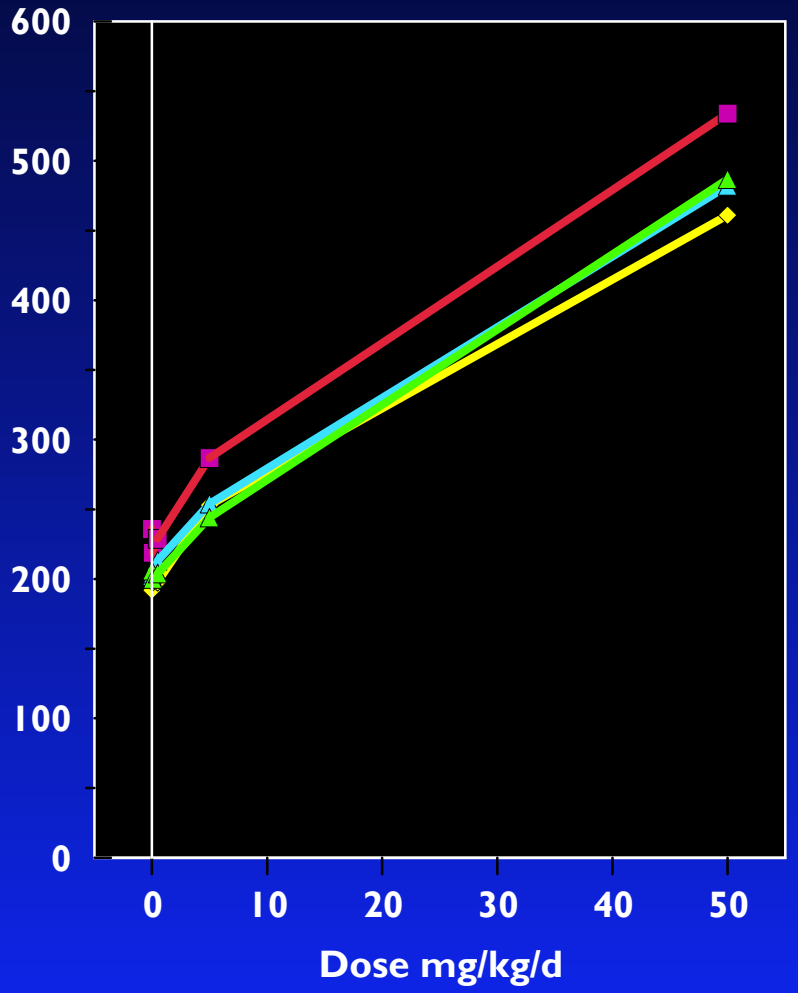
19. Effect of MT on LABC weights. Data from four labs



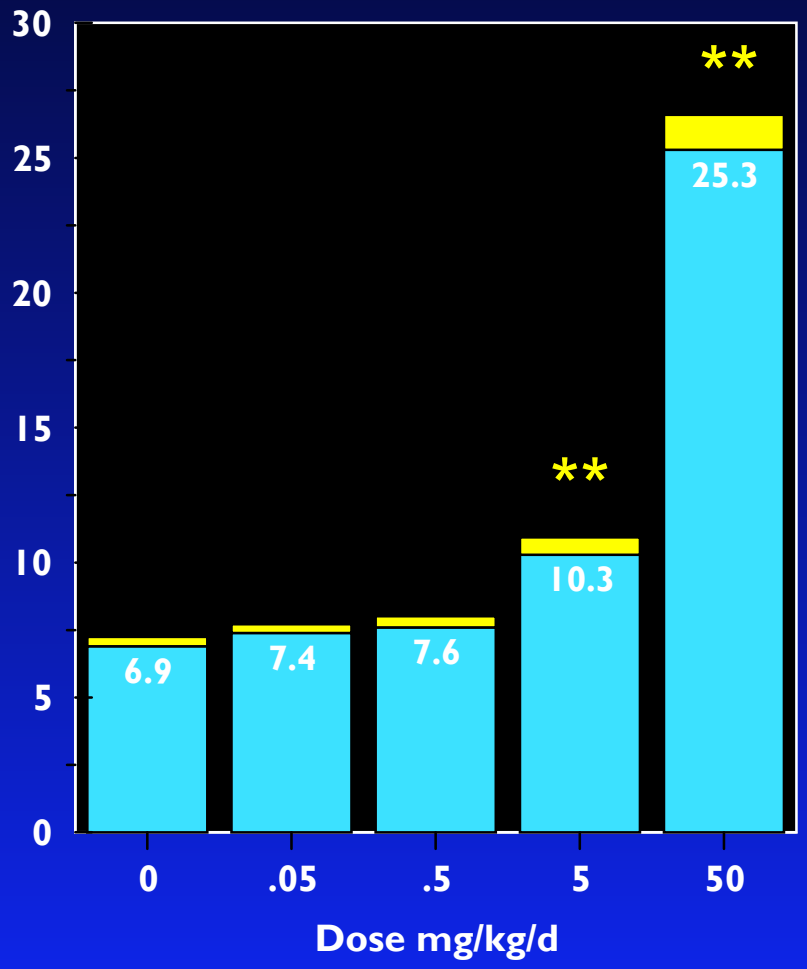


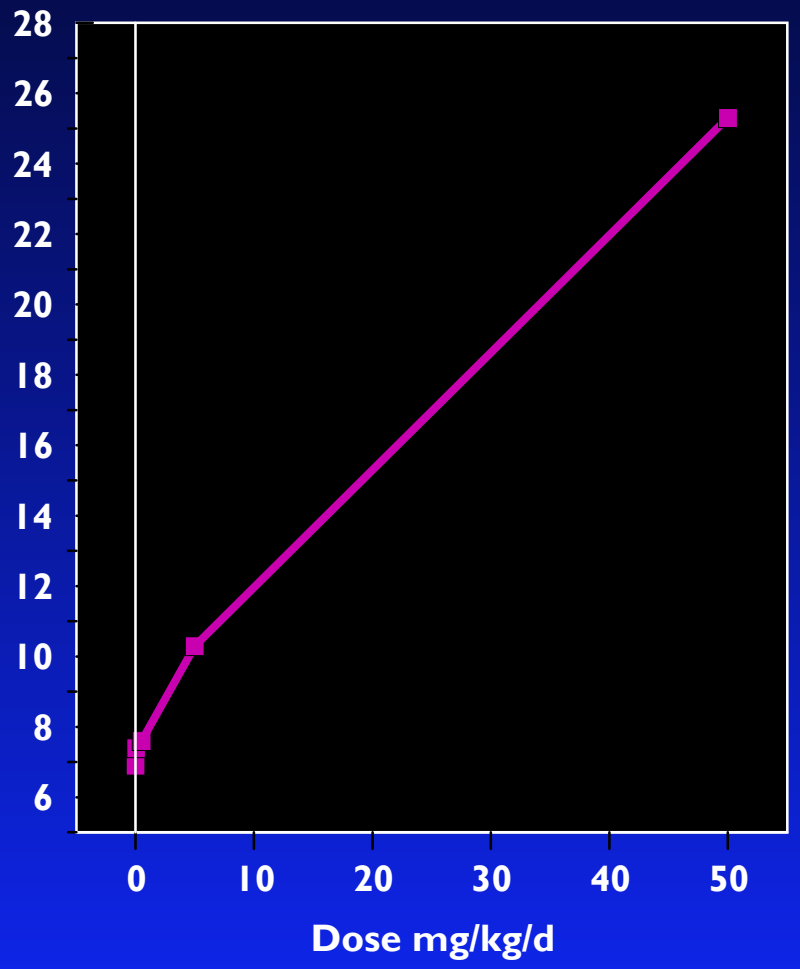
20. Effect of MT on LABC weights. Data from four labs



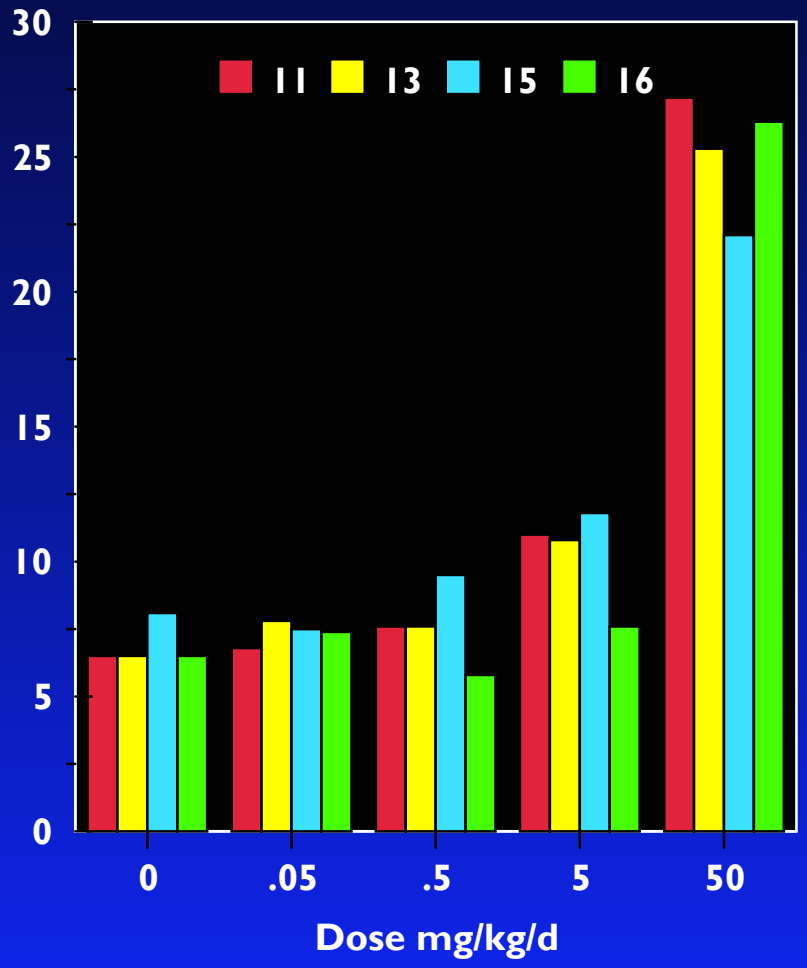


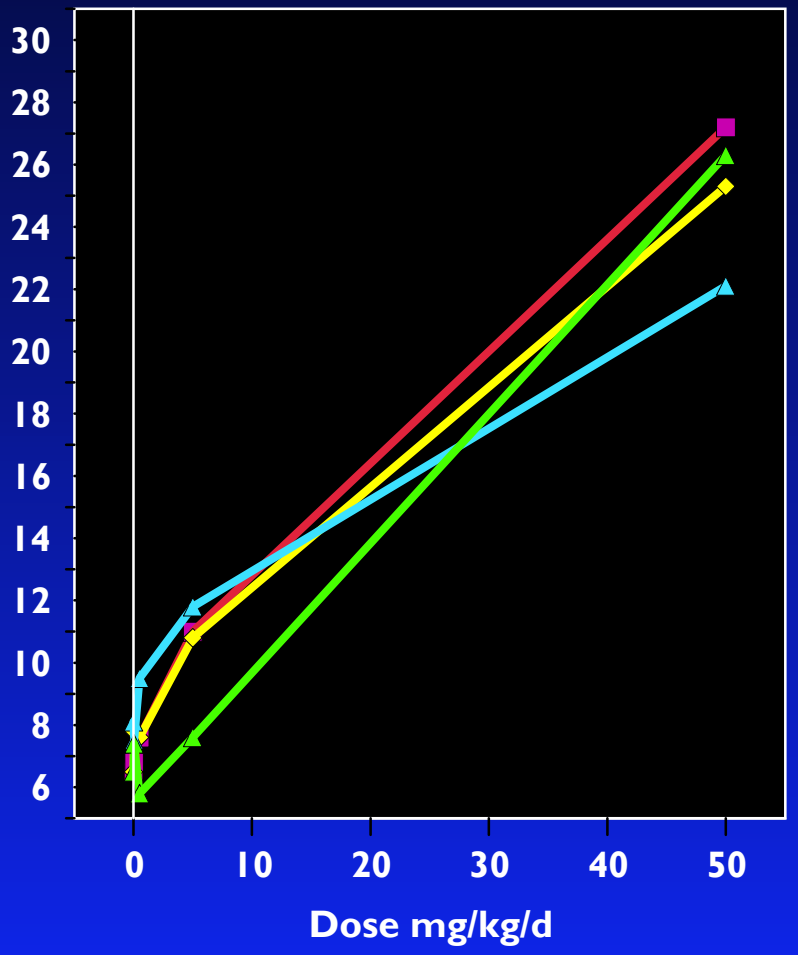
21.Effect of MT on Cowper's gland weights. Data from four labs



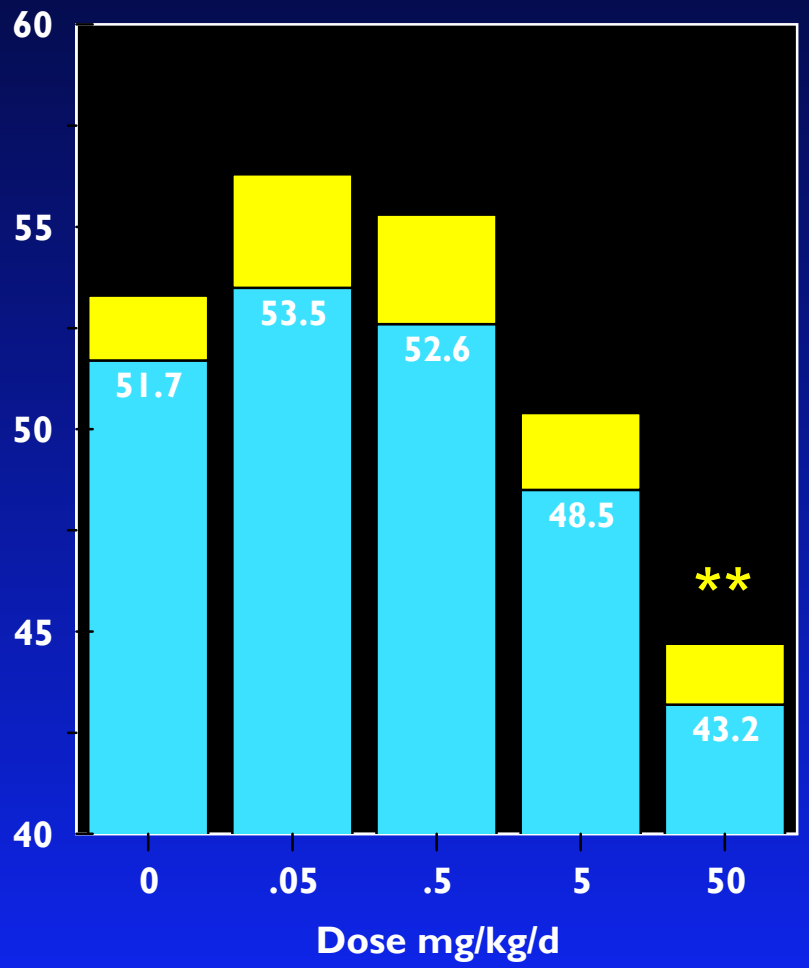


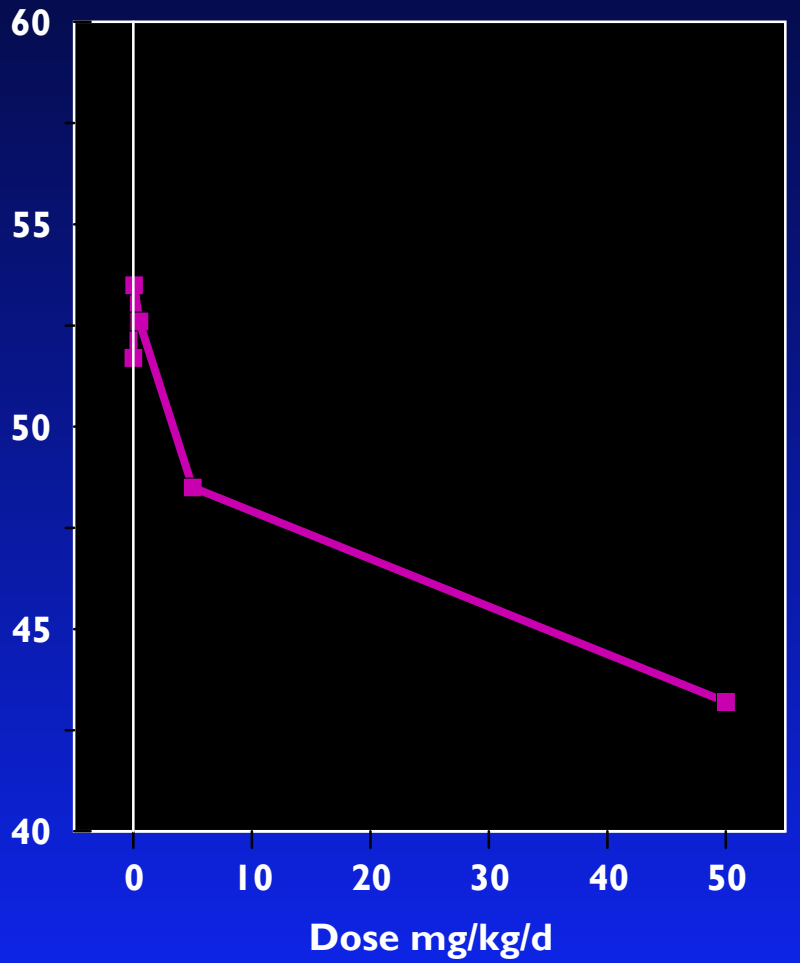
22. Effect of MT on Cowper's gland weights. Data from four labs



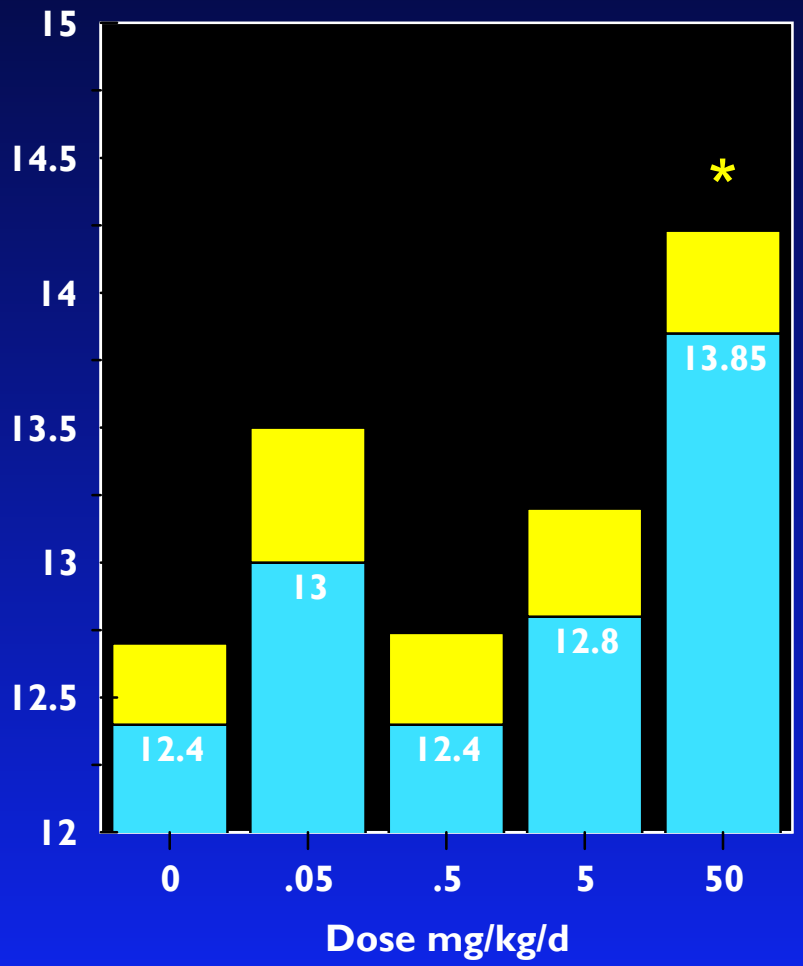


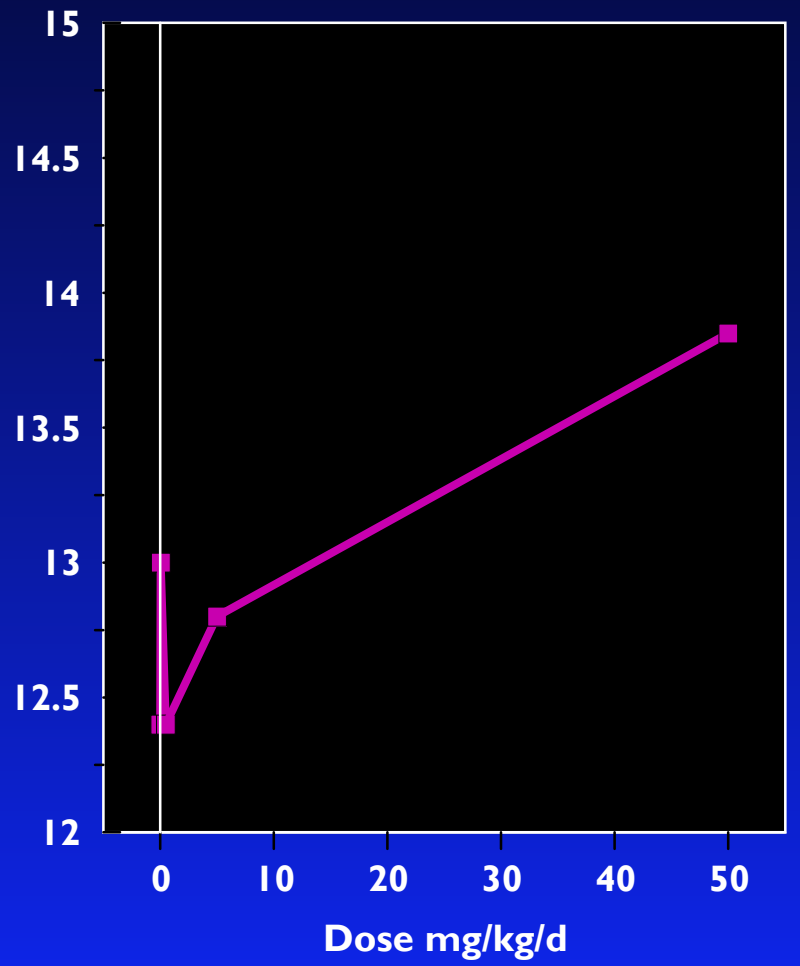
23. Effect of MT on adrenal weights. Data from two labs



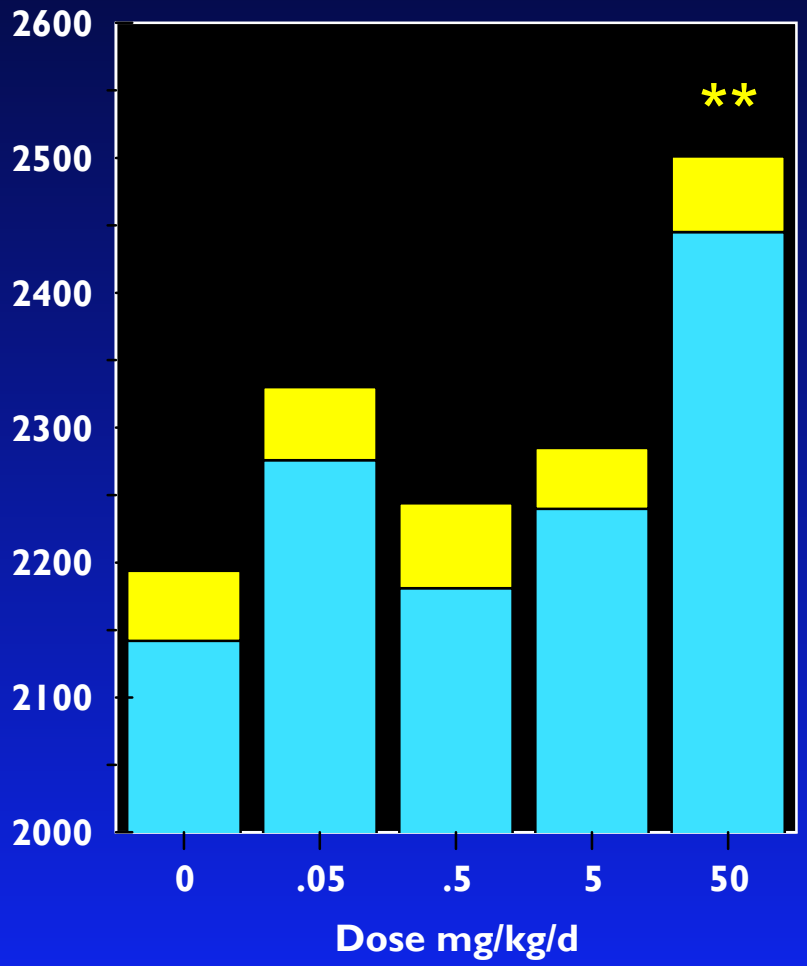


24. Effect of MT on liver weights at necropsy. Data from two labs

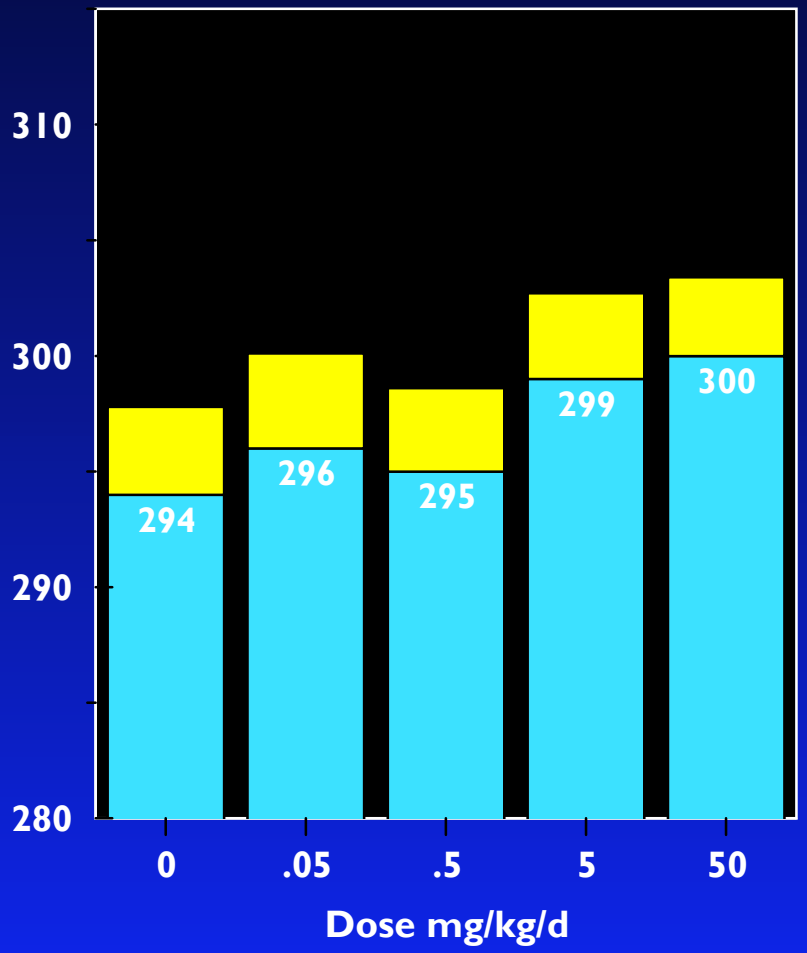


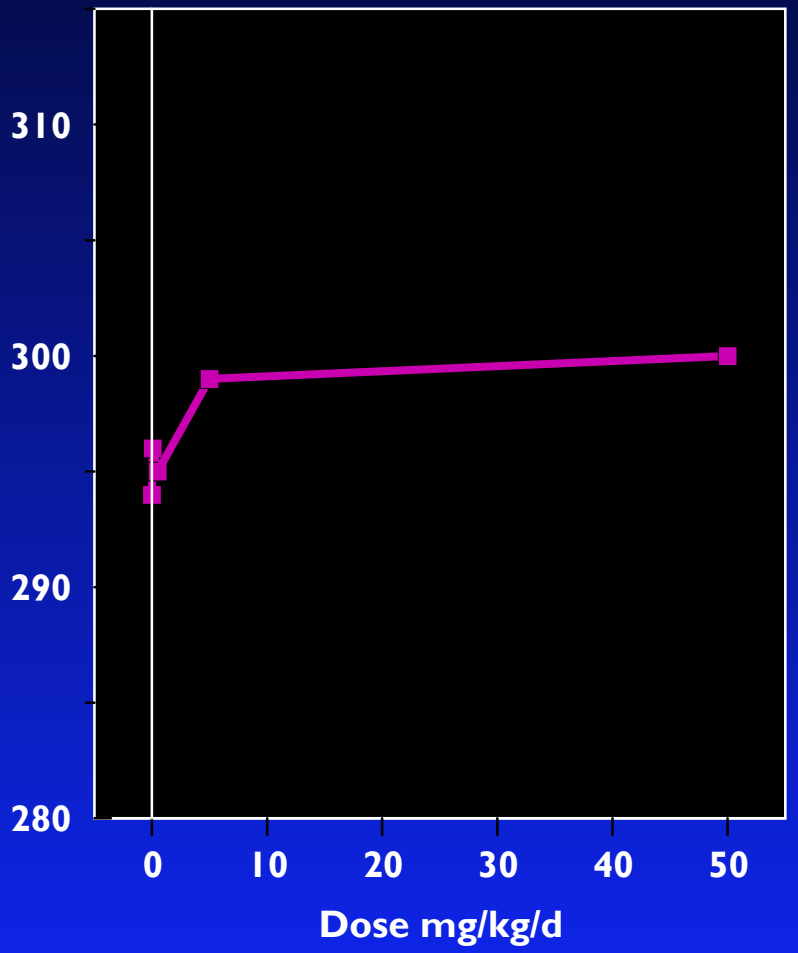


25. Effect of MT on Kidney weights. Data from two labs

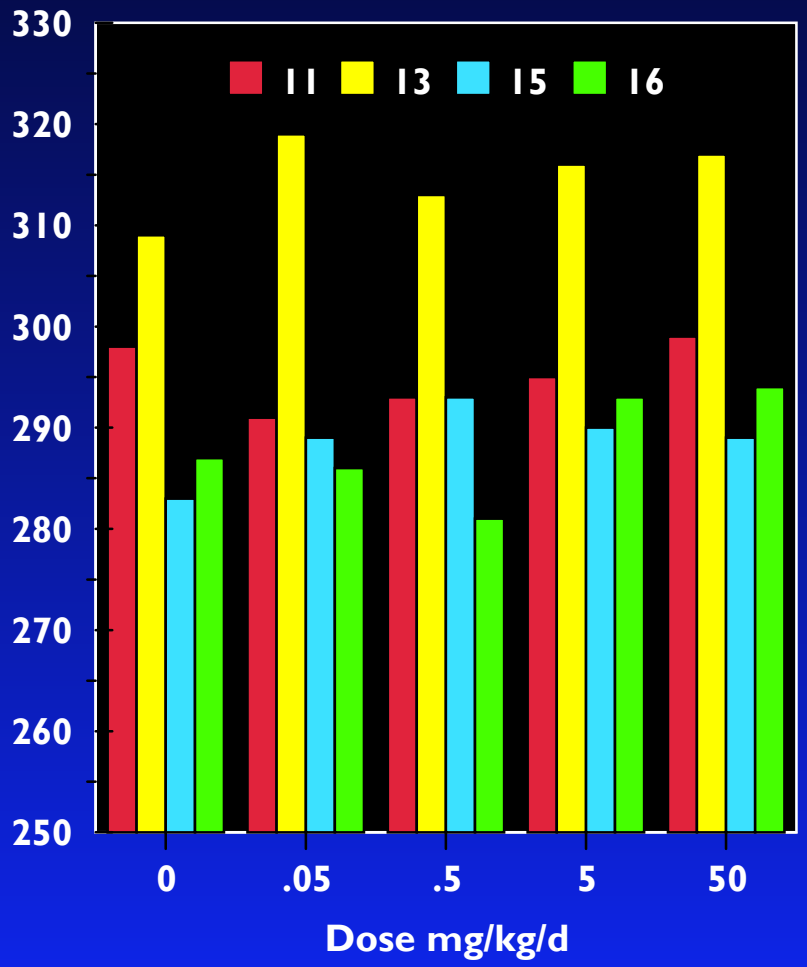


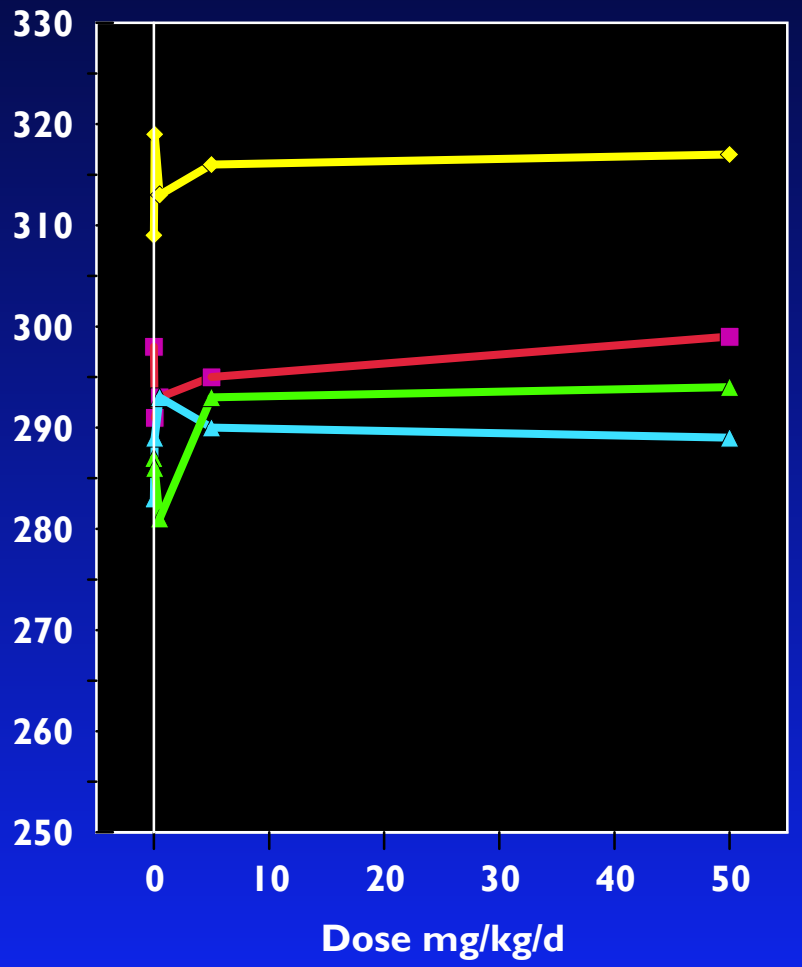
26. Effect of MT on body weights at necropsy. Data from four labs



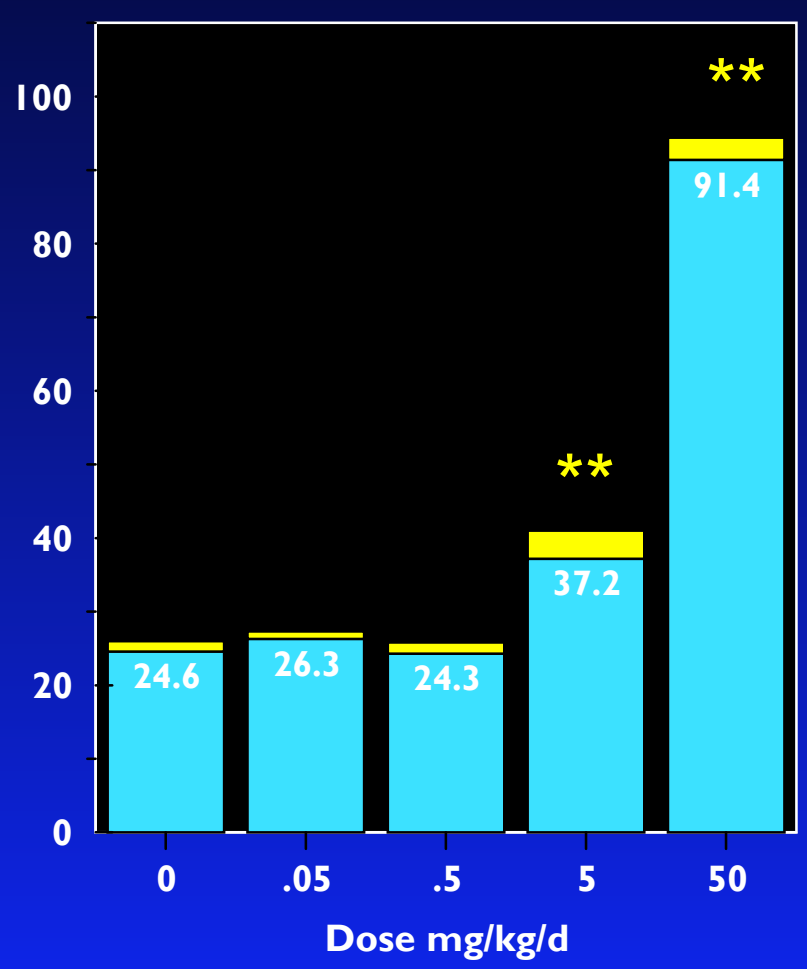


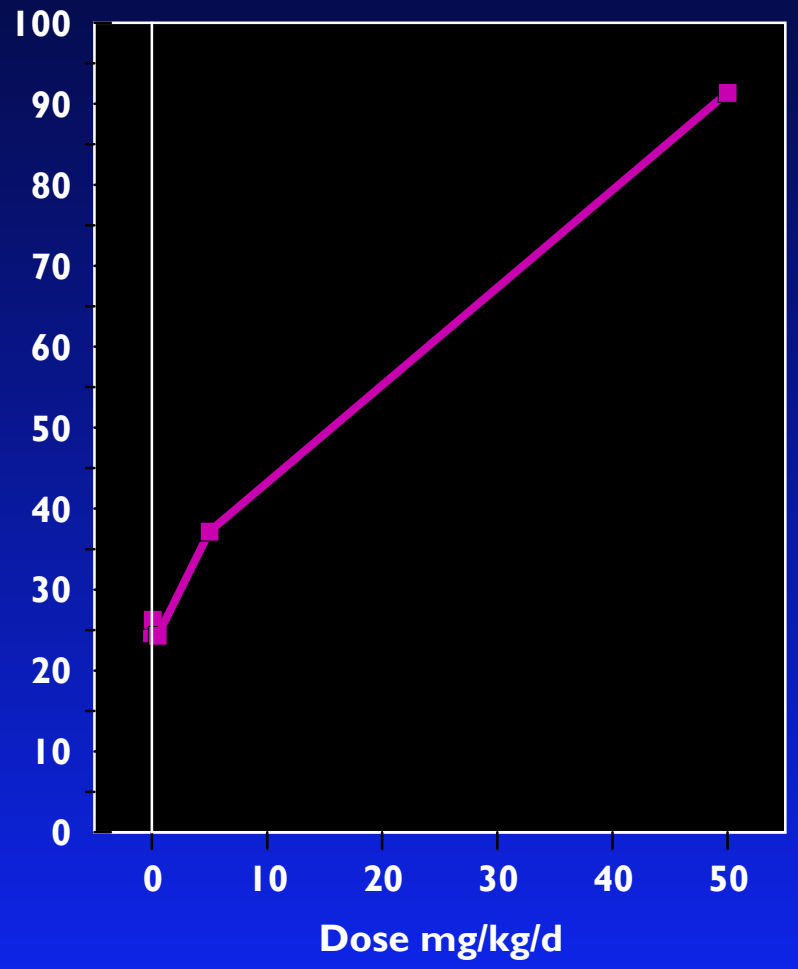
26 b. Effect of MT on body weights at necropsy. Data from four labs



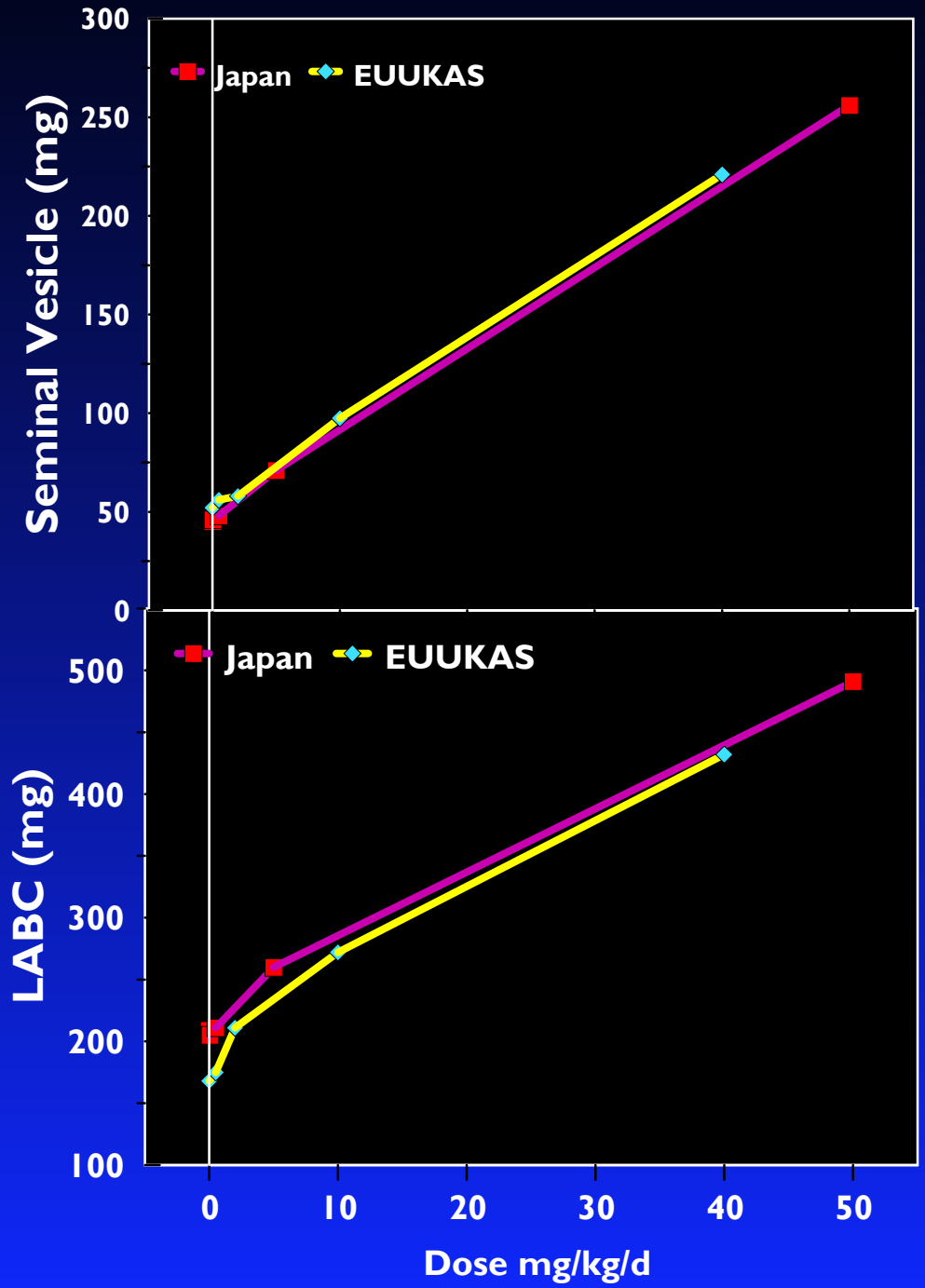


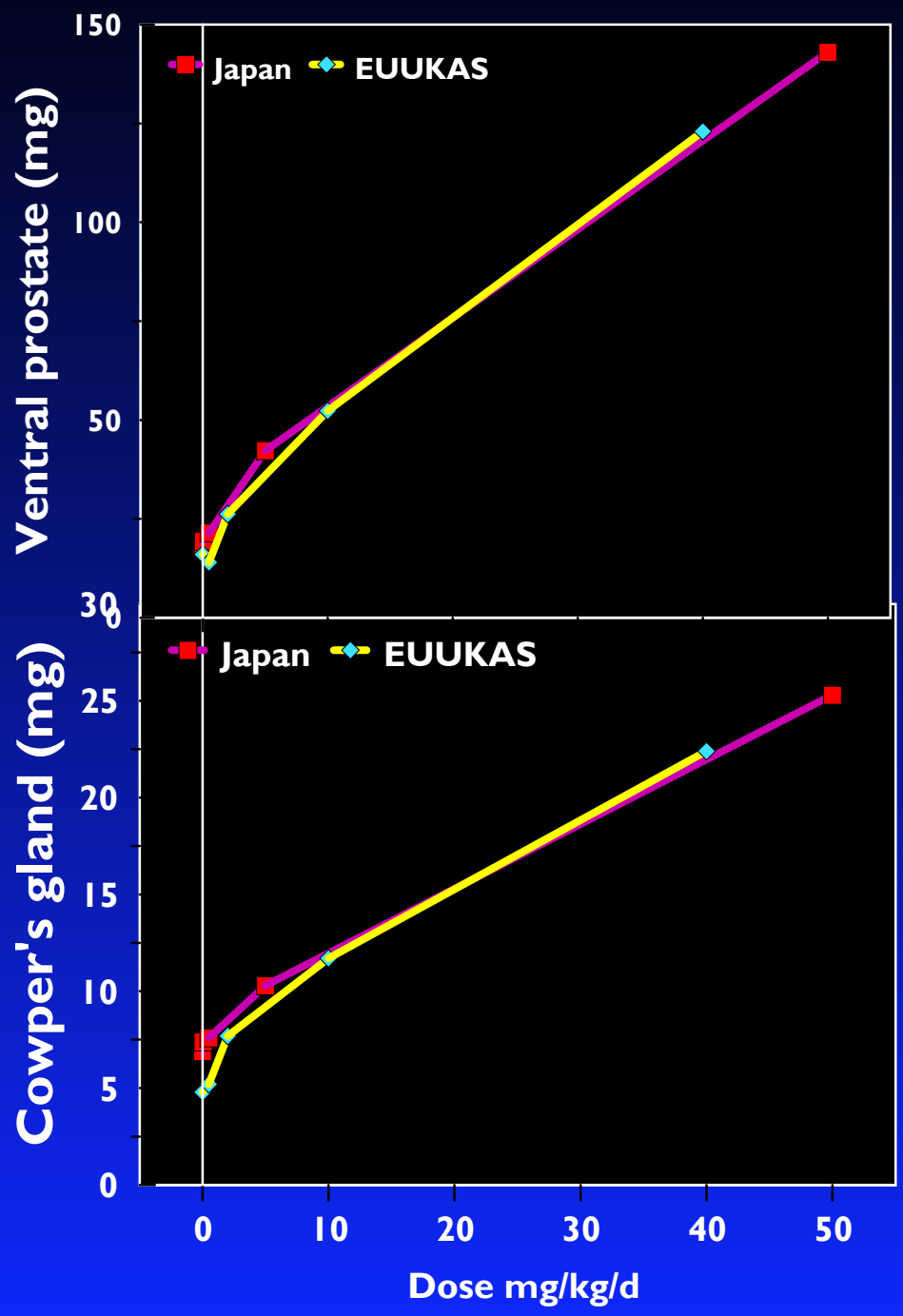
Effect of MT on dorsolateral prostate-fixed weights. Data from one lab





27. Effects of MT from Japan versus EUUKAS on androgen- dependent organ weights for four tissues. The results are nearly identical.

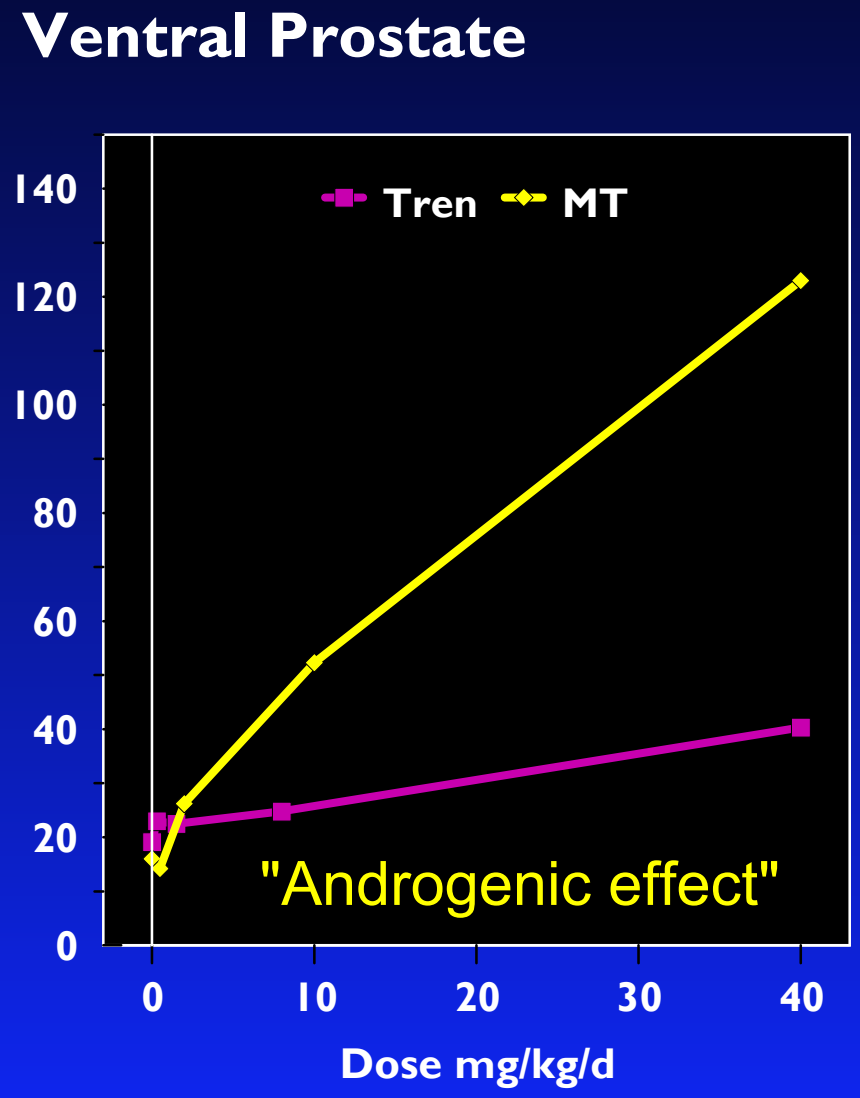


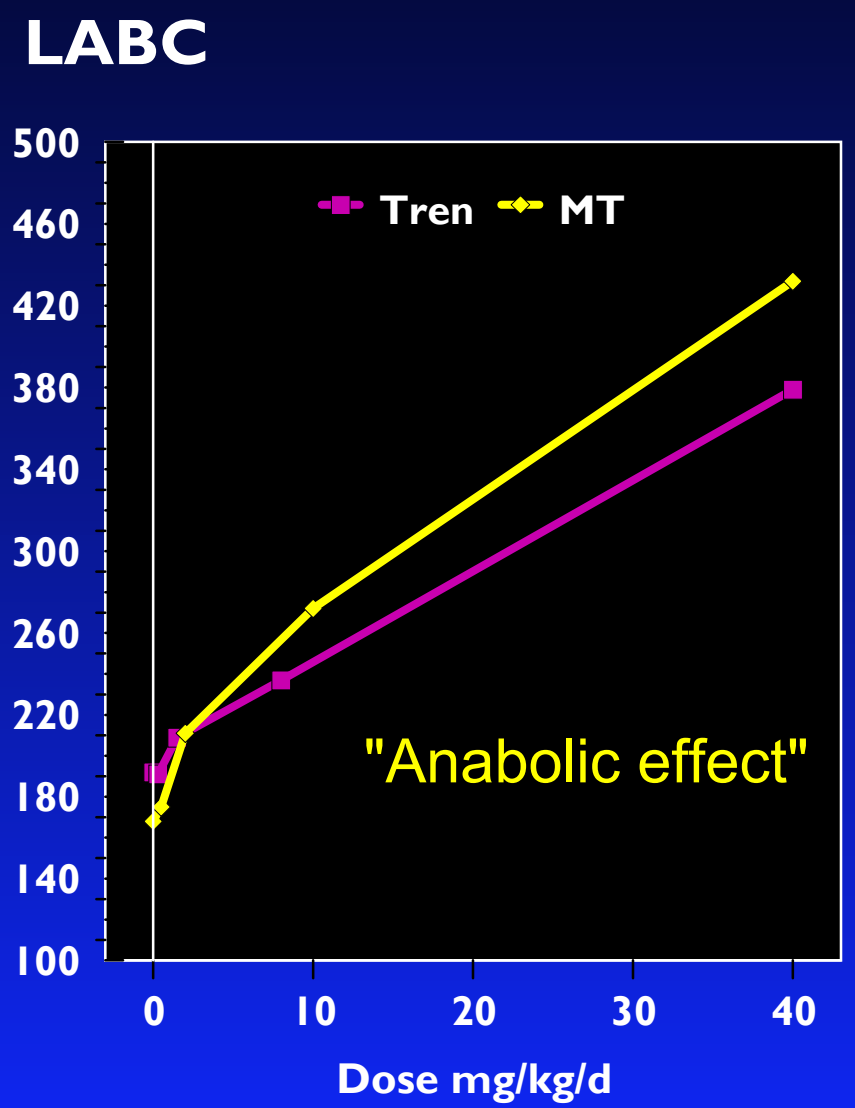


Phase 2
OECD Hershberger Assay
Interlaboratory study

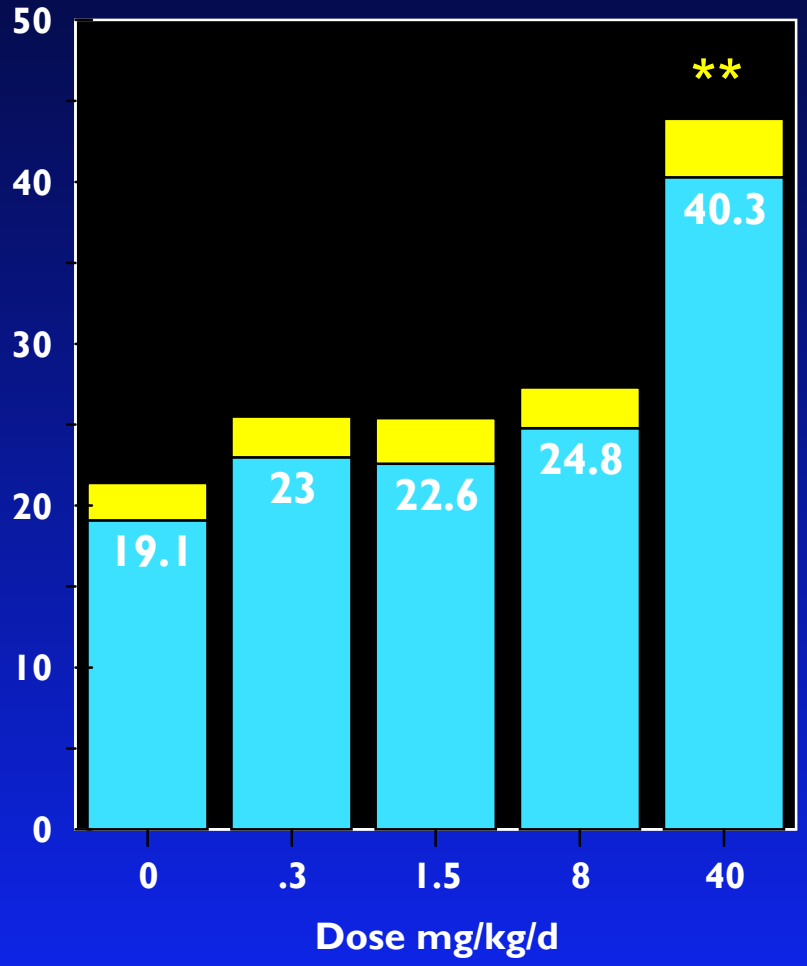
Trenbolone

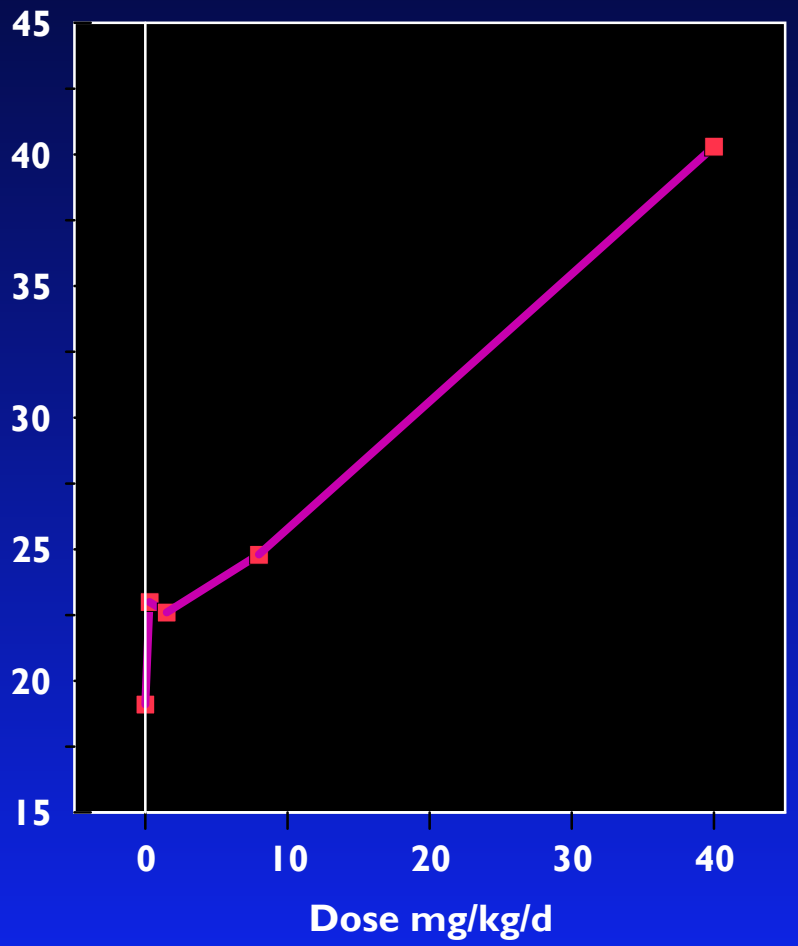
28. Effects of Trenbolone and MT on androgen- dependent organ. Data from EUUKAS studies. Oral Trenbolone is more effective in stimulating LABC weight than VP weight as compared to MT.



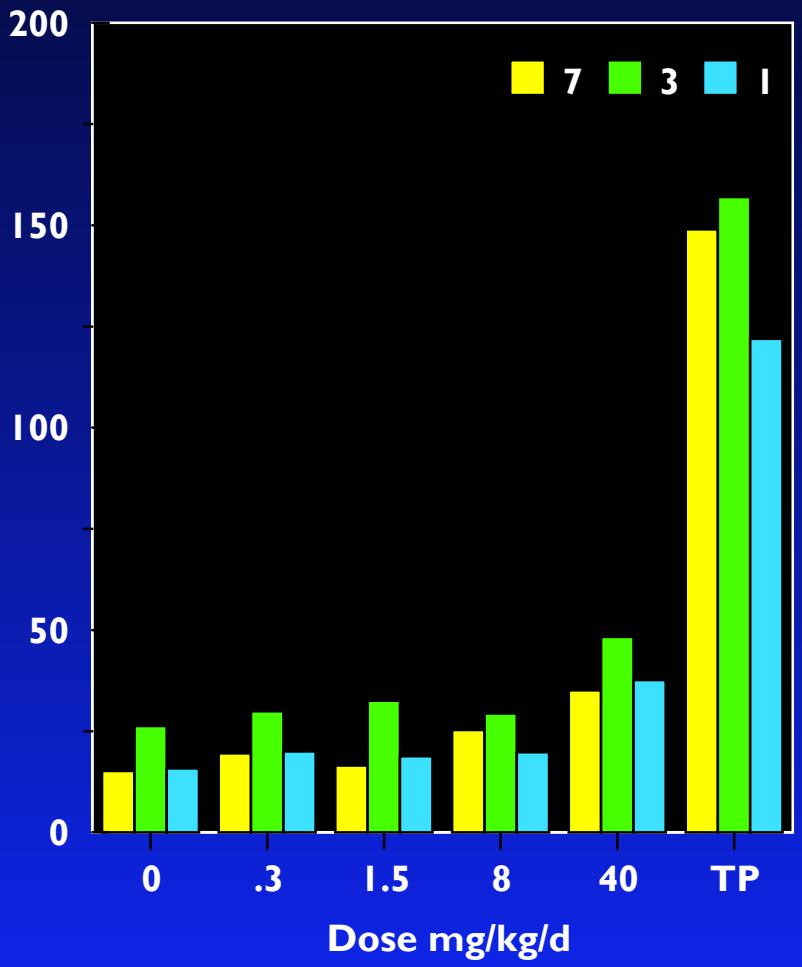


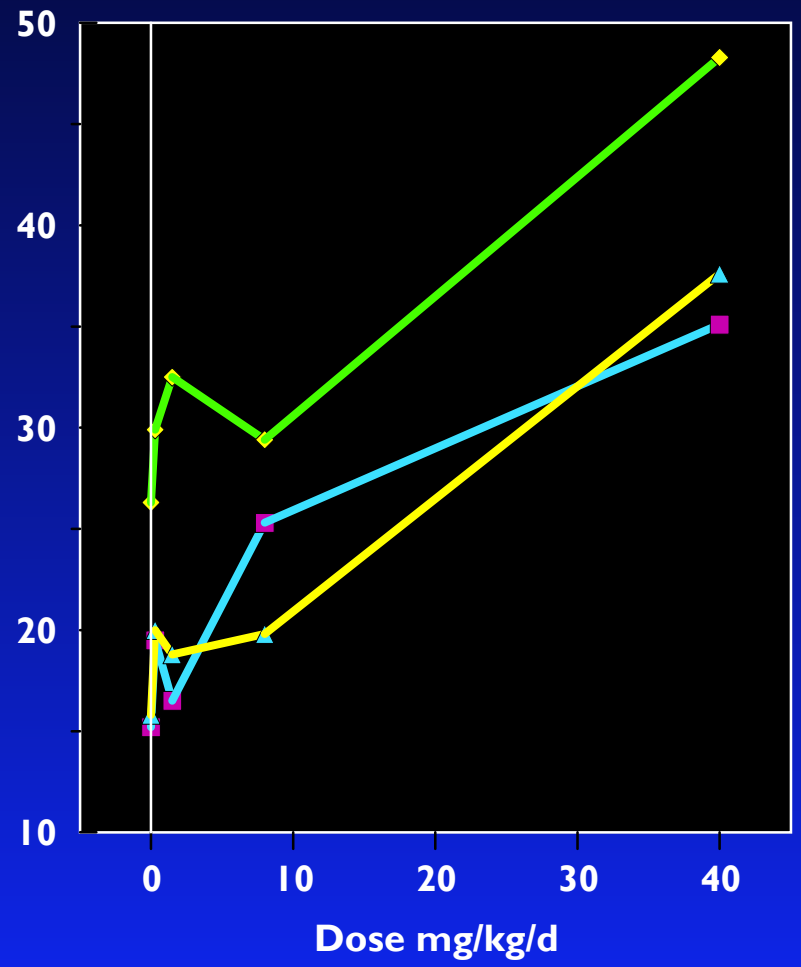
29.Effect of Trenbolone on Ventral Prostate weights. Data from 3 labs



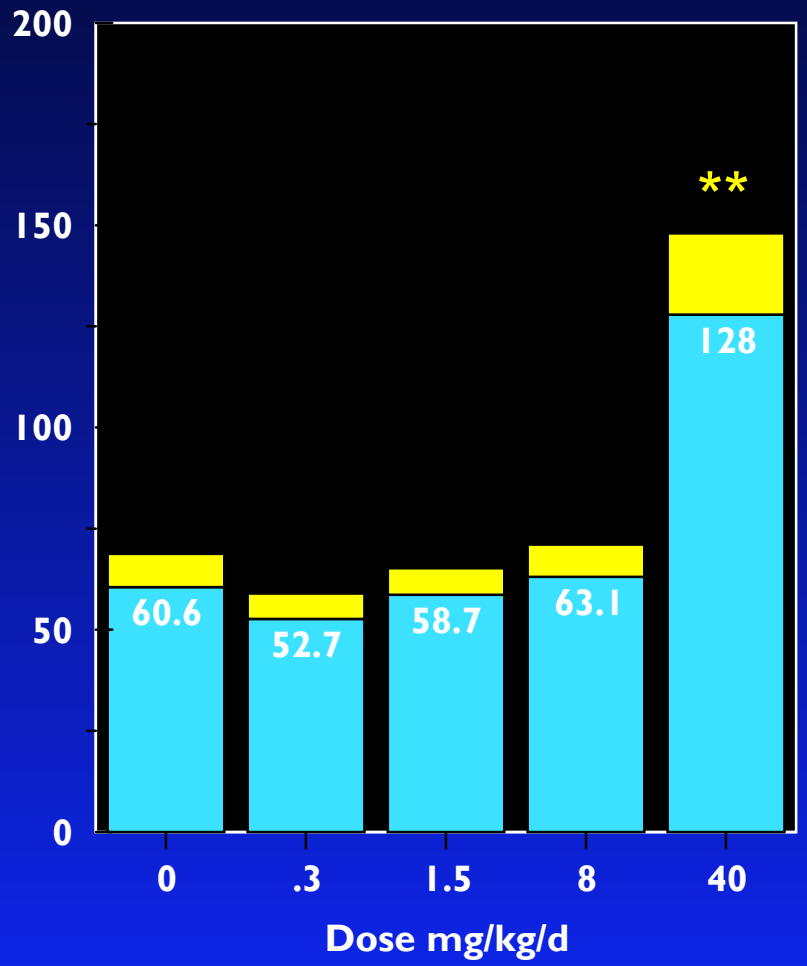


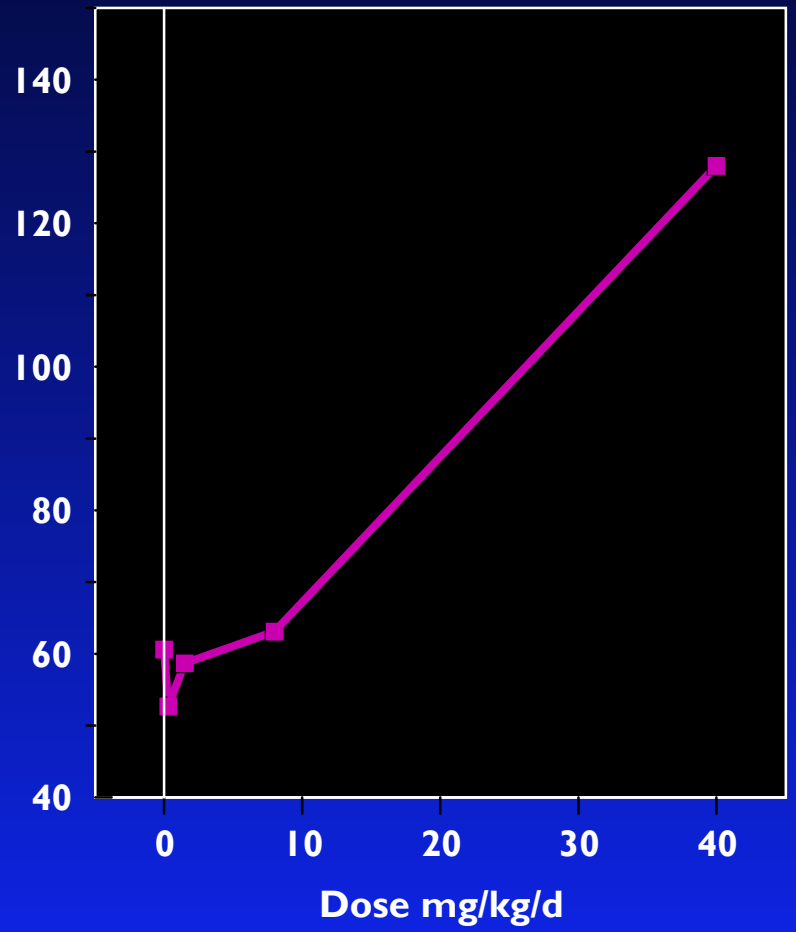
30. Effect of Trenbolone on VP weights. Data from 3 labs



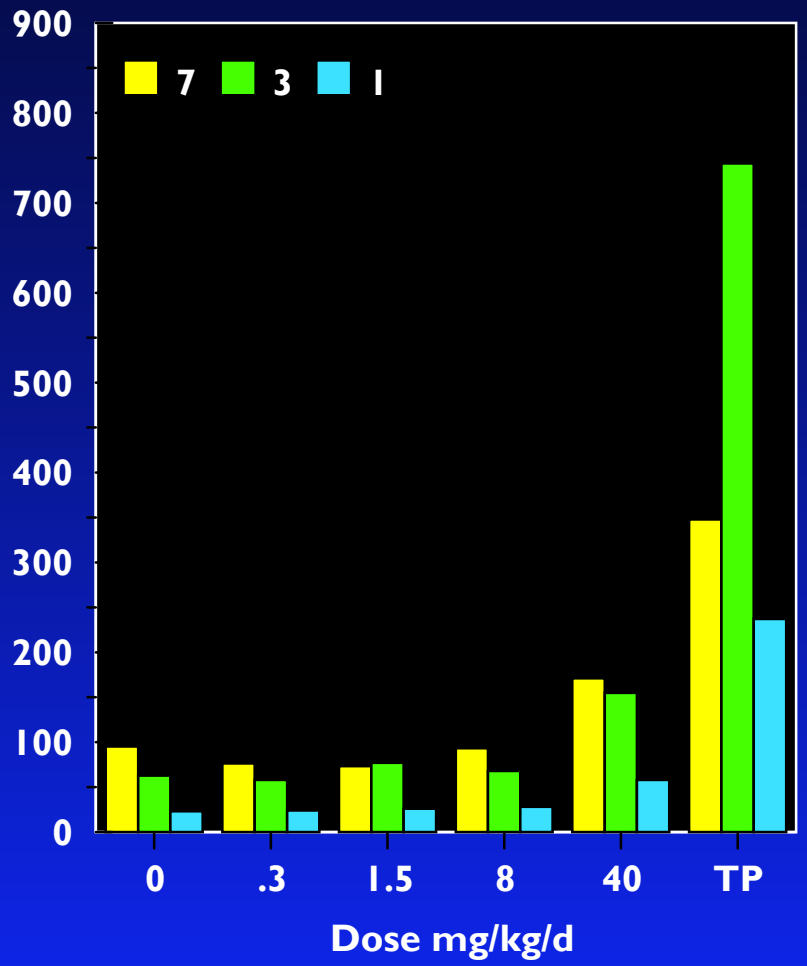


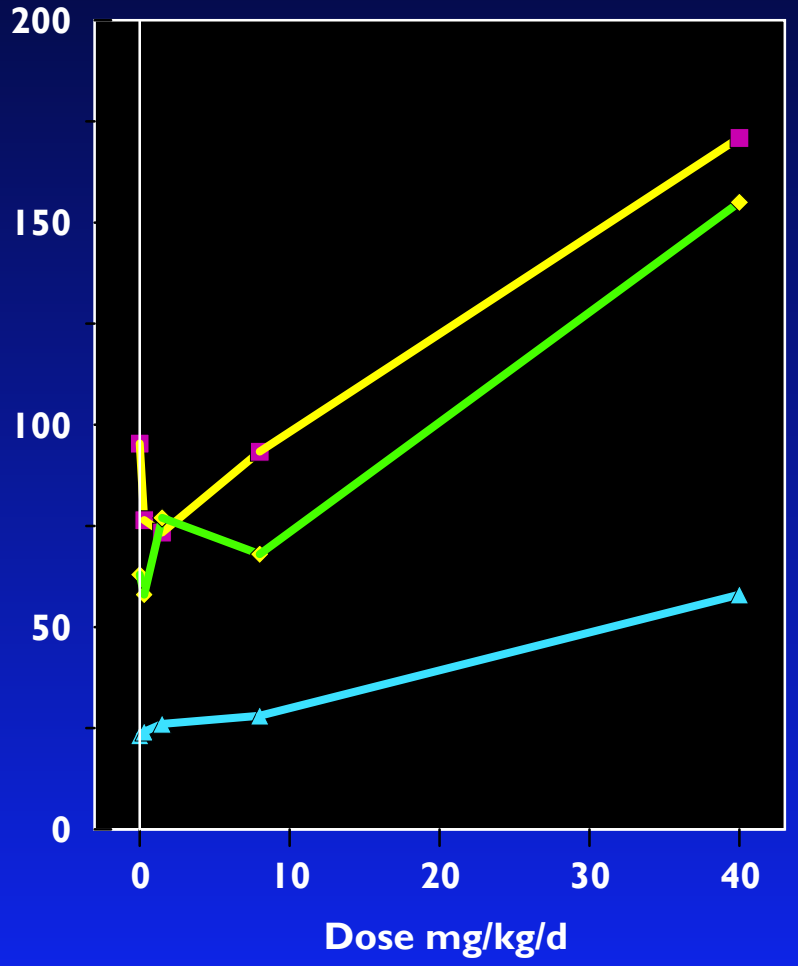
31. Effect of Trenbolone on Seminal Vesicle weights. Data from 3 labs



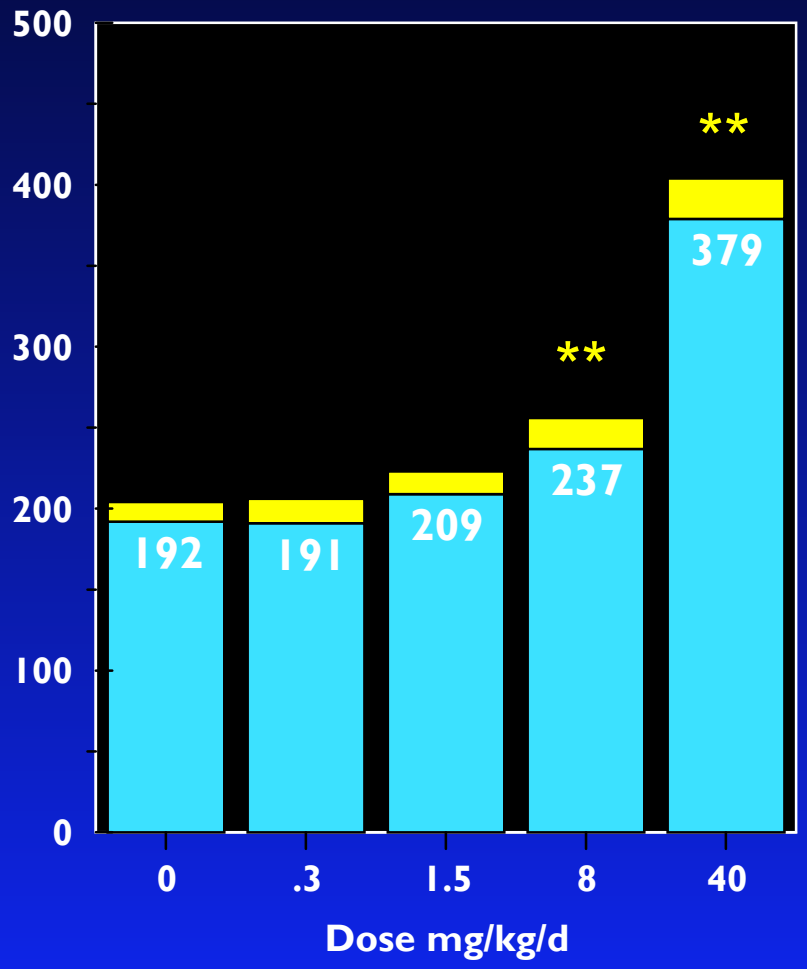


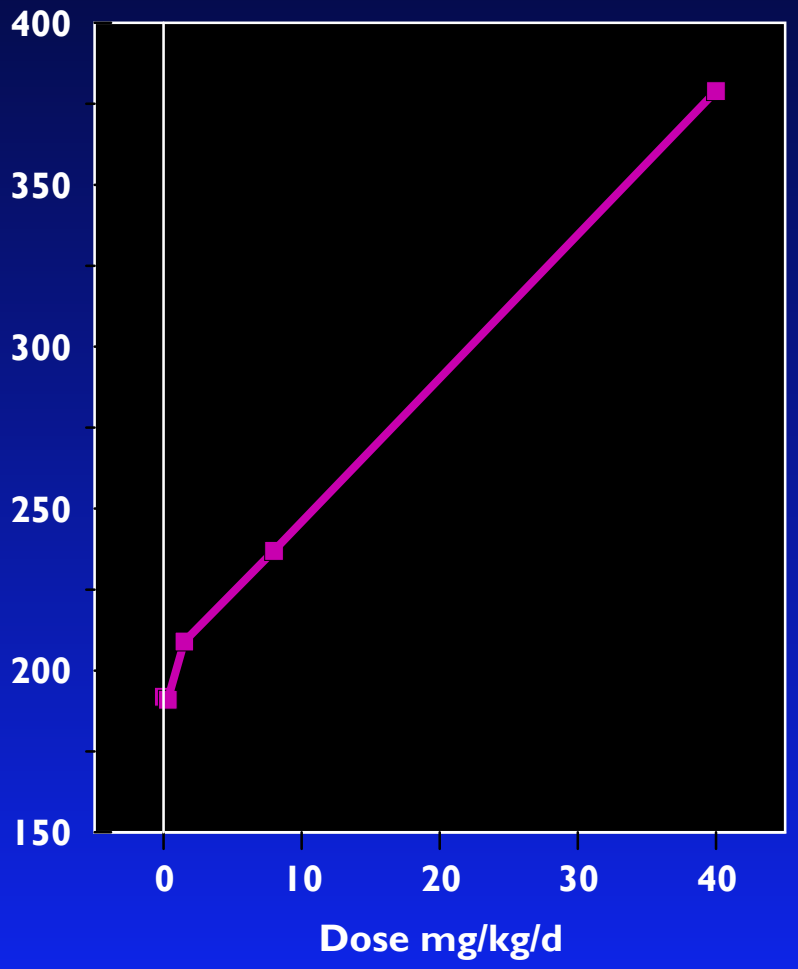
32. Effect of Trenbolone on Seminal Vesicle weights. Data from 3 labs



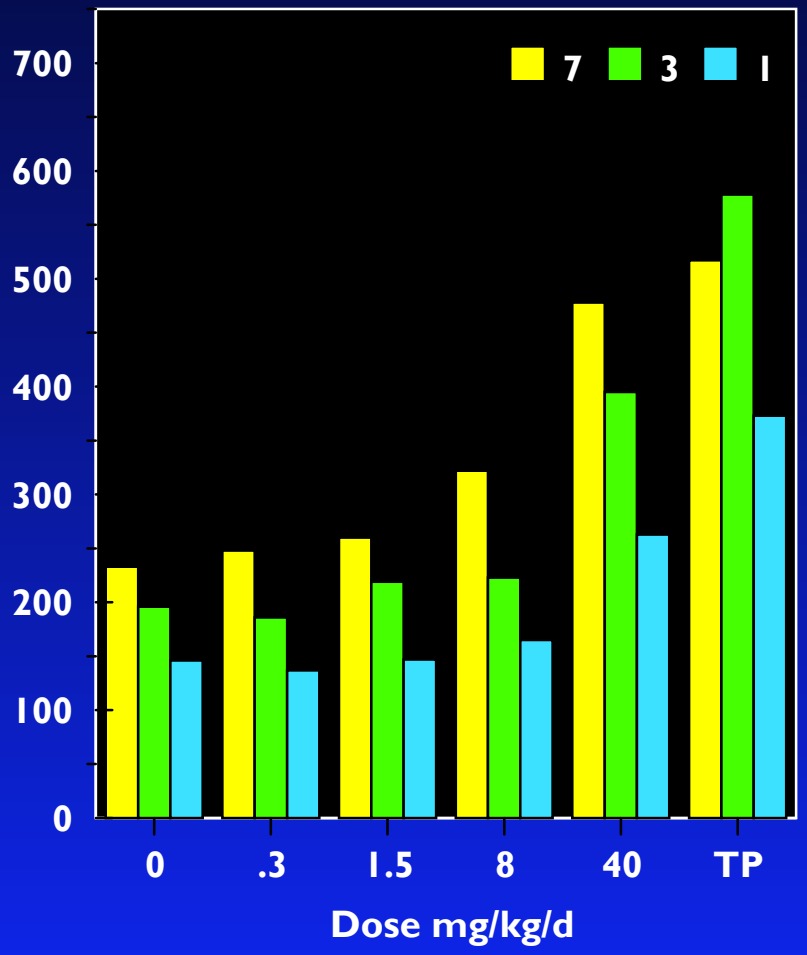


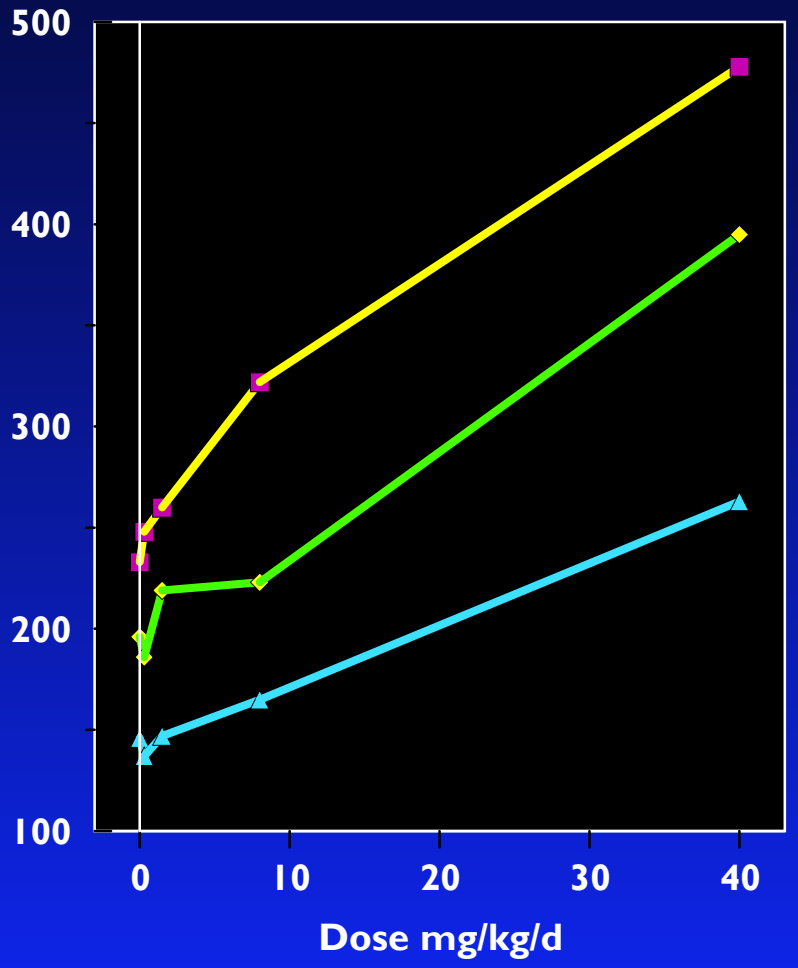
33. Effect of Trenbolone on LABC weights. Data from 3 labs



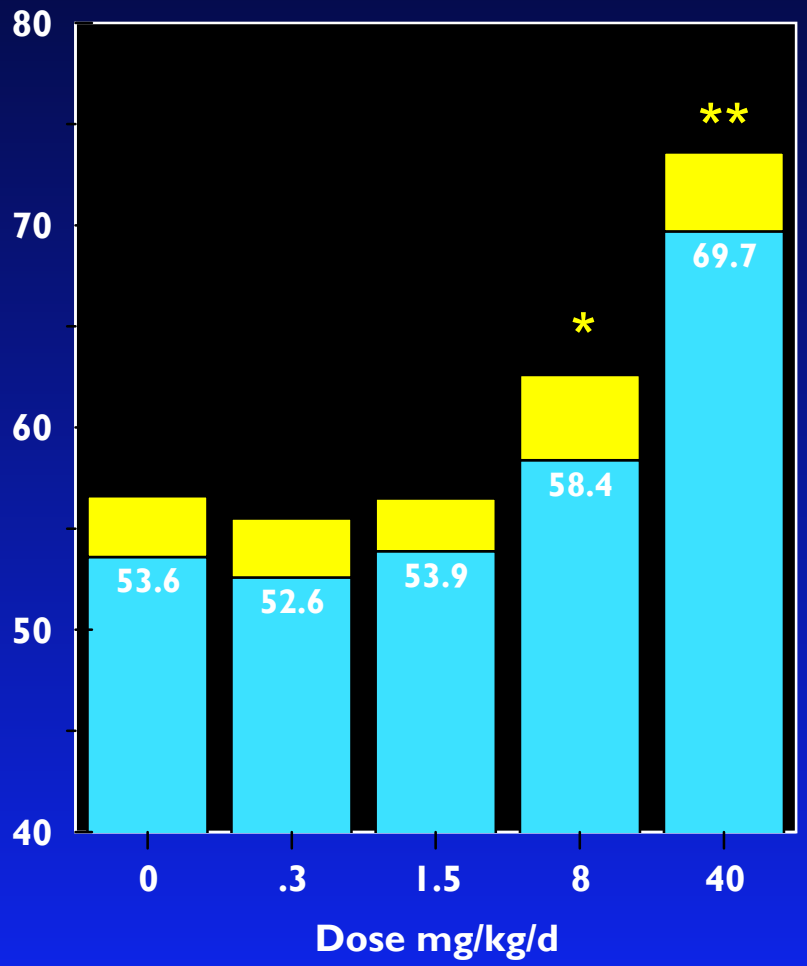


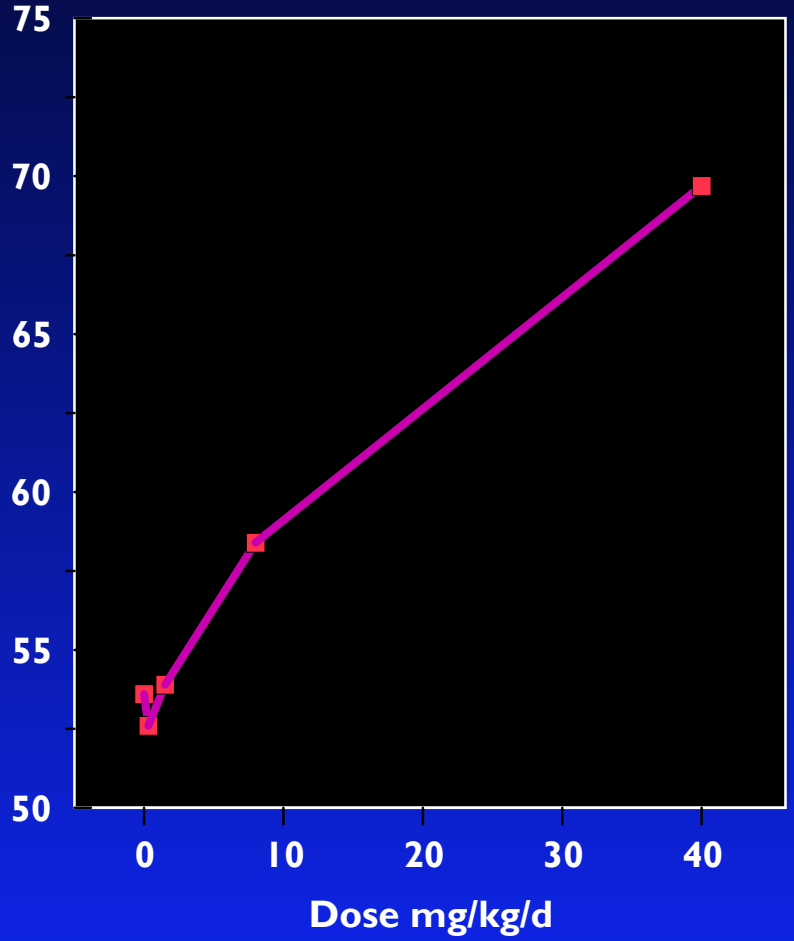
34. Effect of Trenbolone on LABC weights. Data from 3 labs



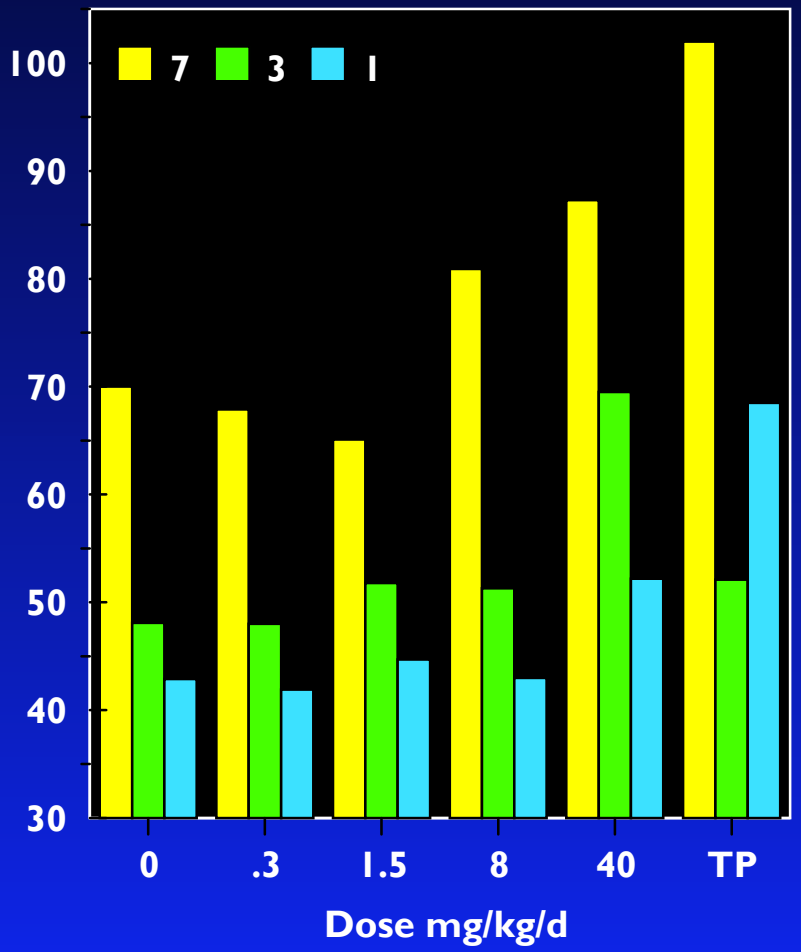


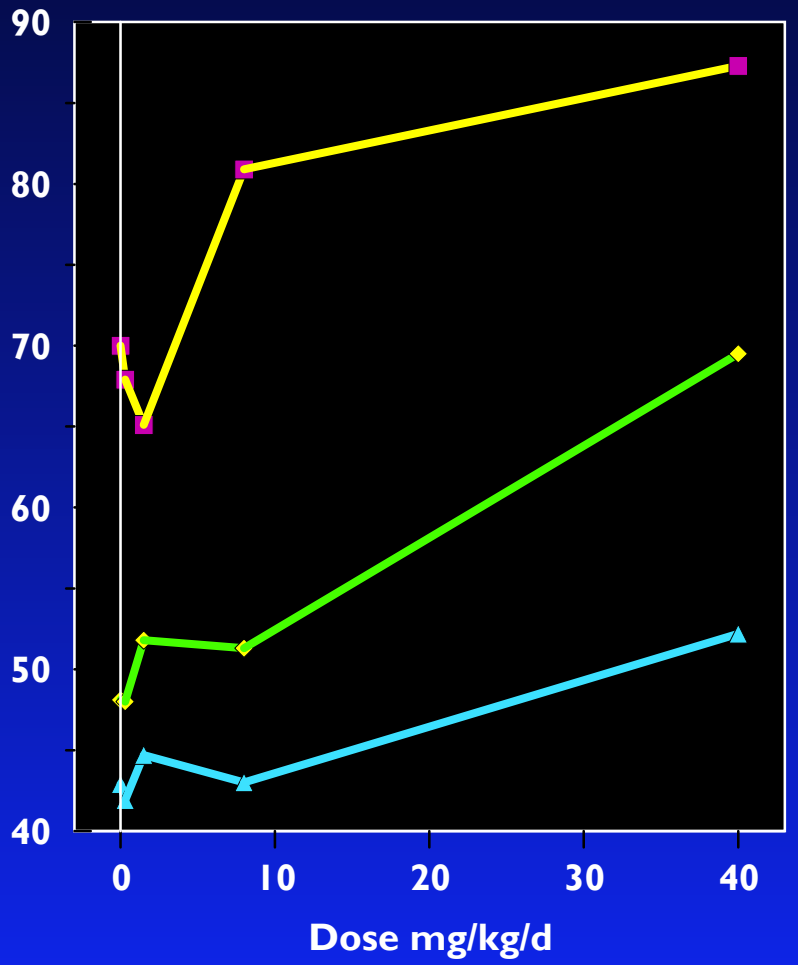
35. Effect of Trenbolone on Glans penis weights. Data from 3 labs



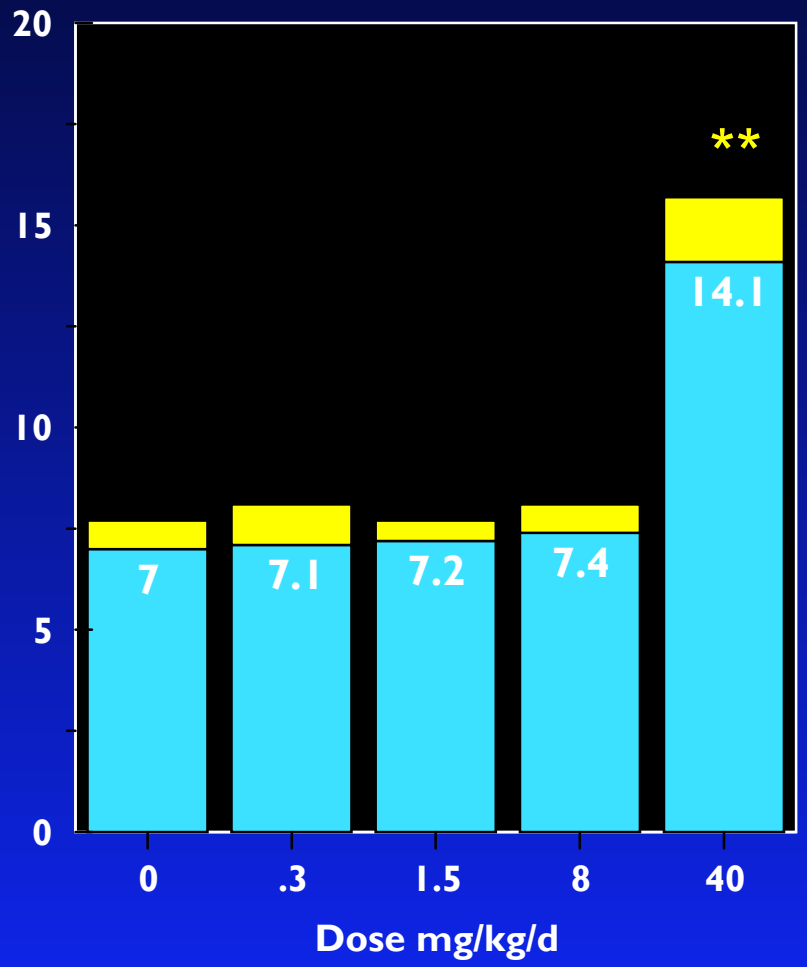


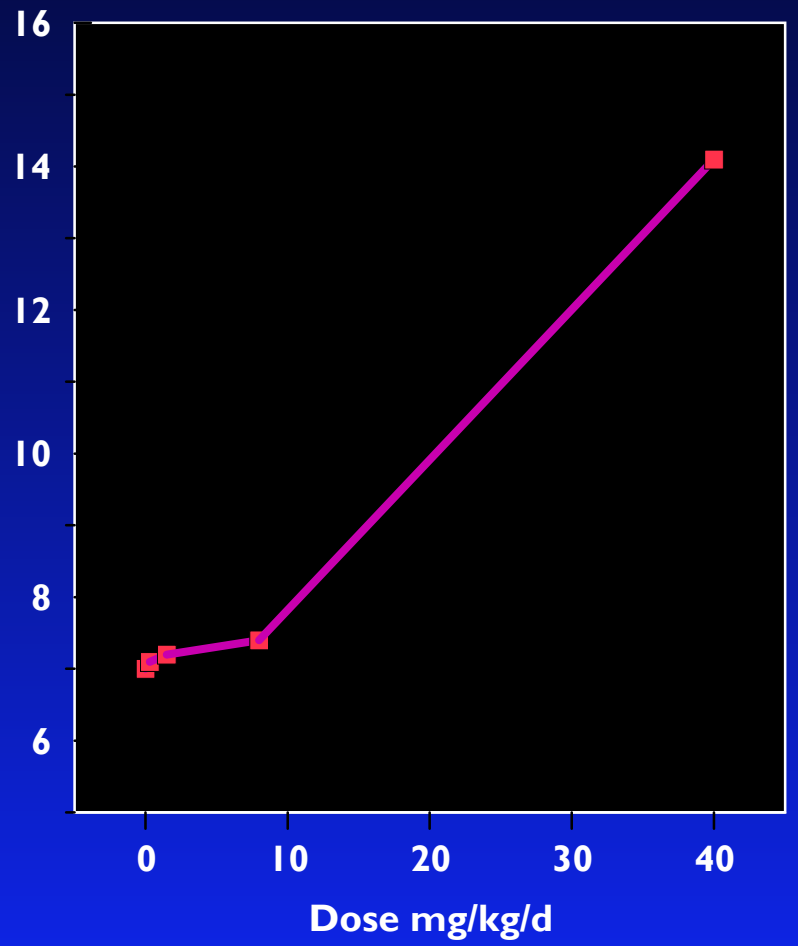
36. Effect of Trenbolone on Glans Penis weights. Data from 3 labs



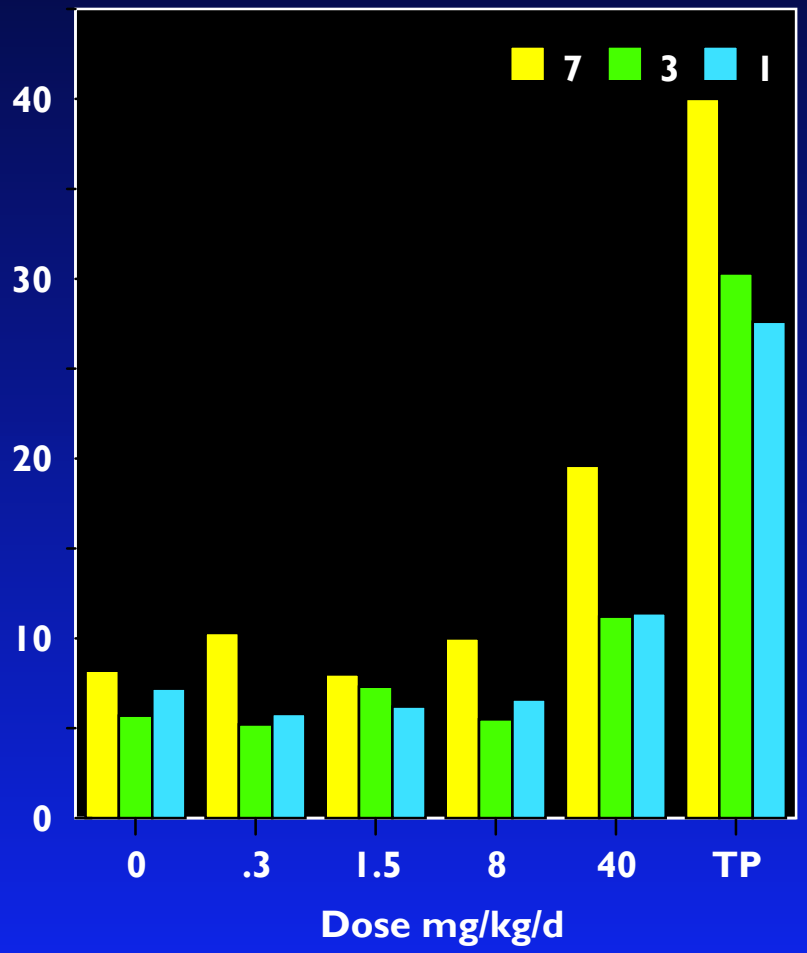


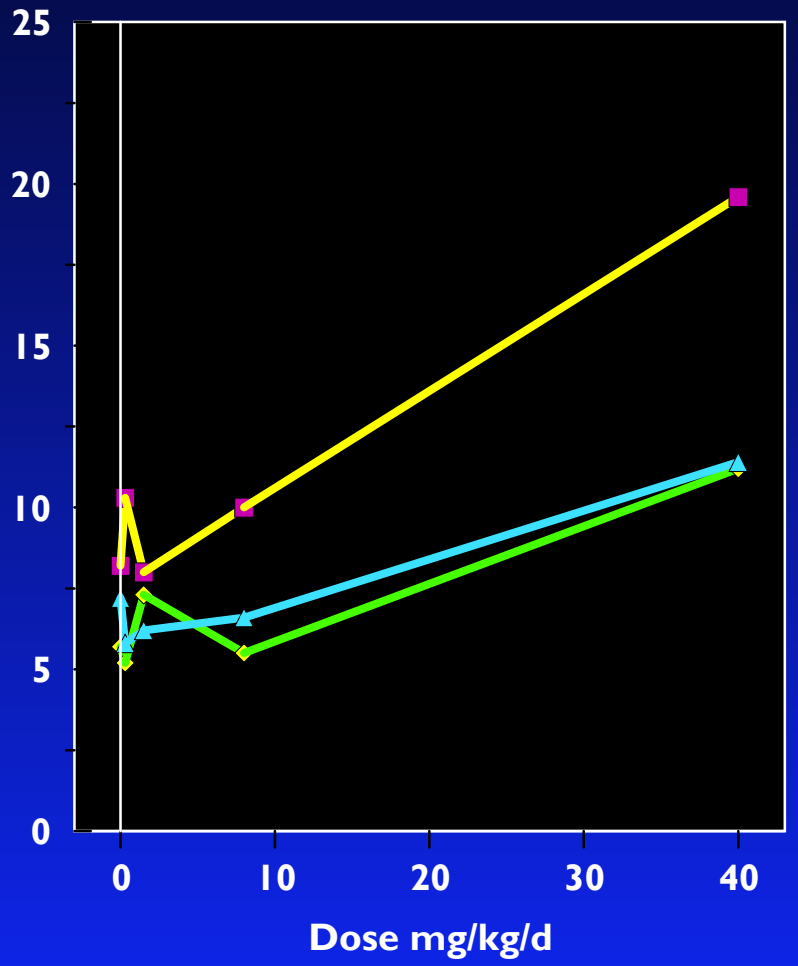
37. Effect of Trenbolone on Cowper's gland weights. Data from 3 labs



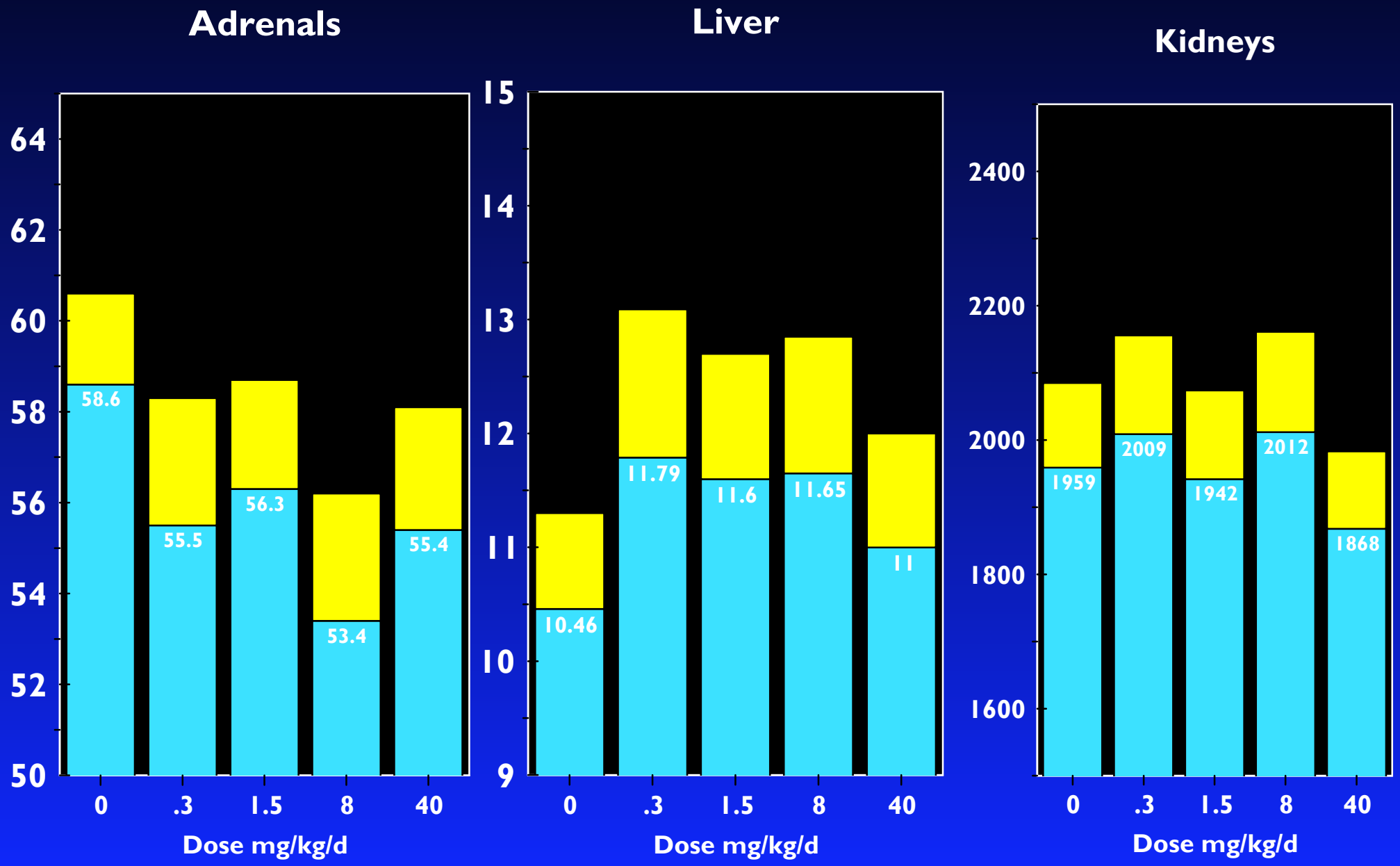


38. Effect of Trenbolone on Cowper's gland weights. Data from 3 labs

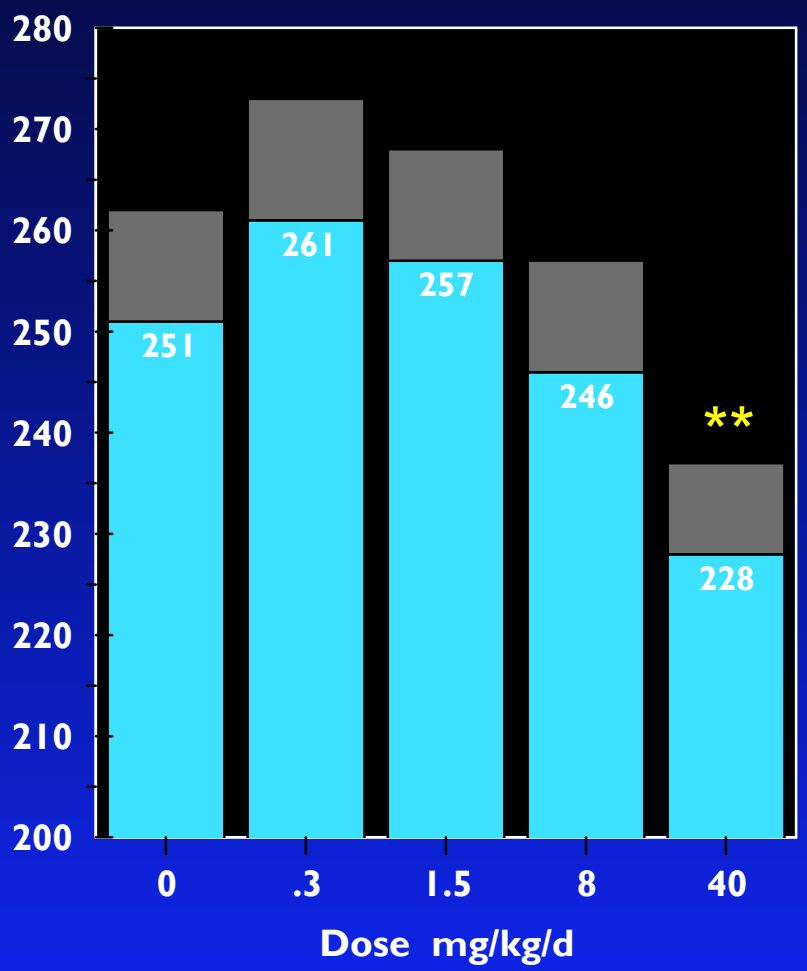


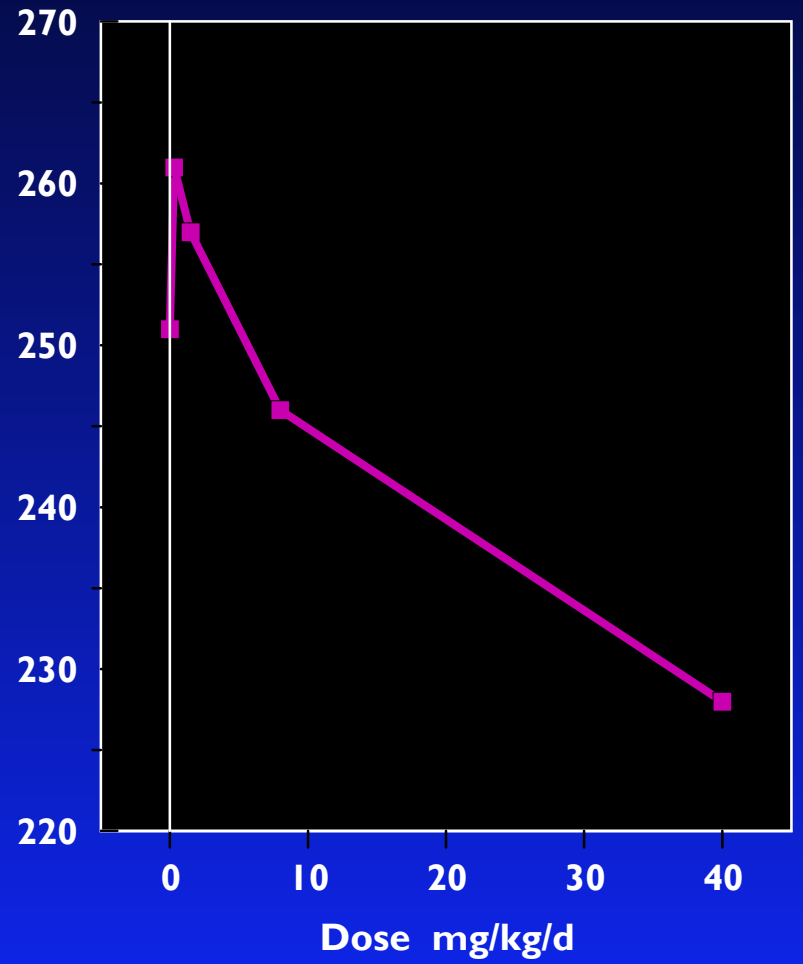


39. Lack of effect of Trenbolone on Adrenal, Liver and Kidney weights. Data from 3 labs



40. Effects of Trenbolone on Body weight at necropsy

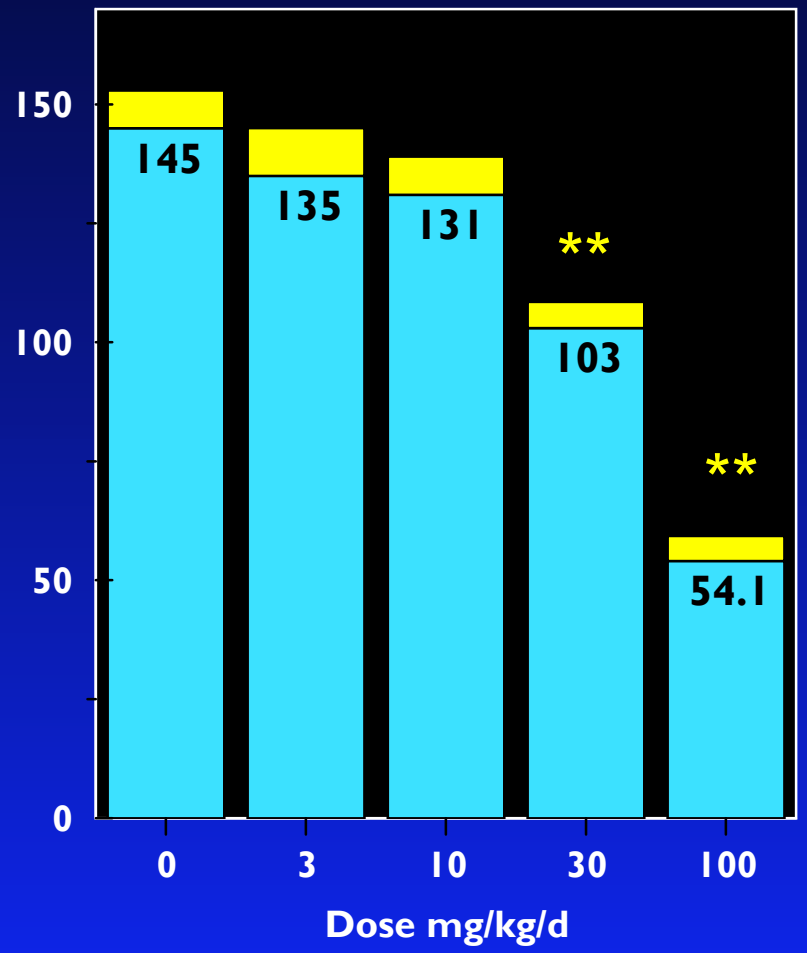


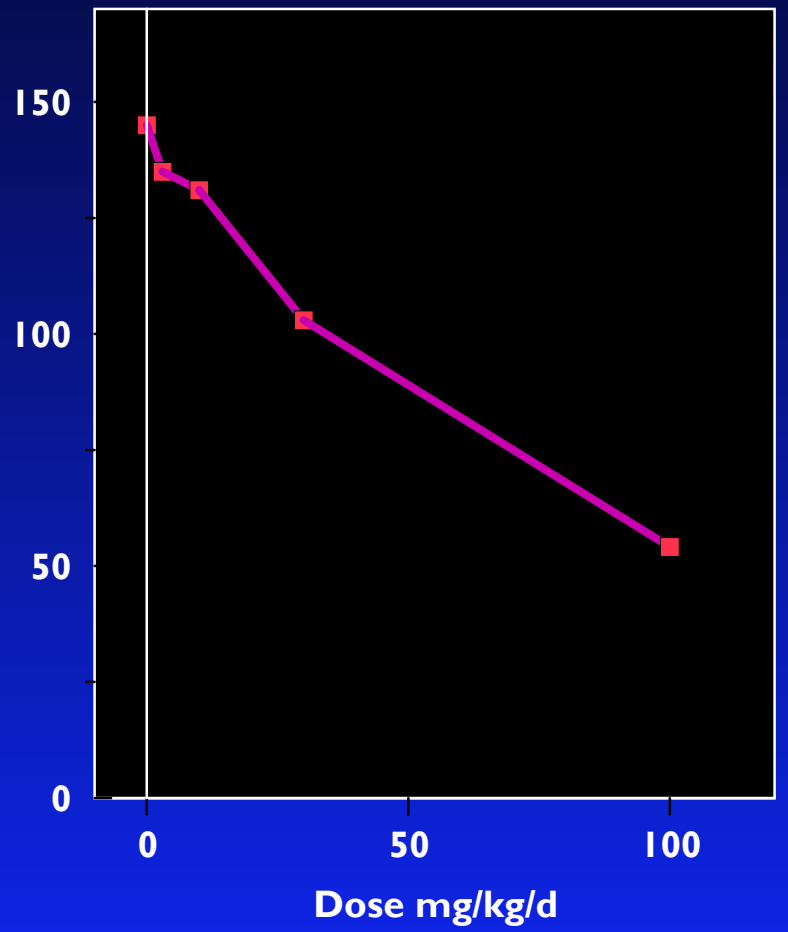


Phase 2
OECD Hershberger Assay Interlaboratory study EUUKAS

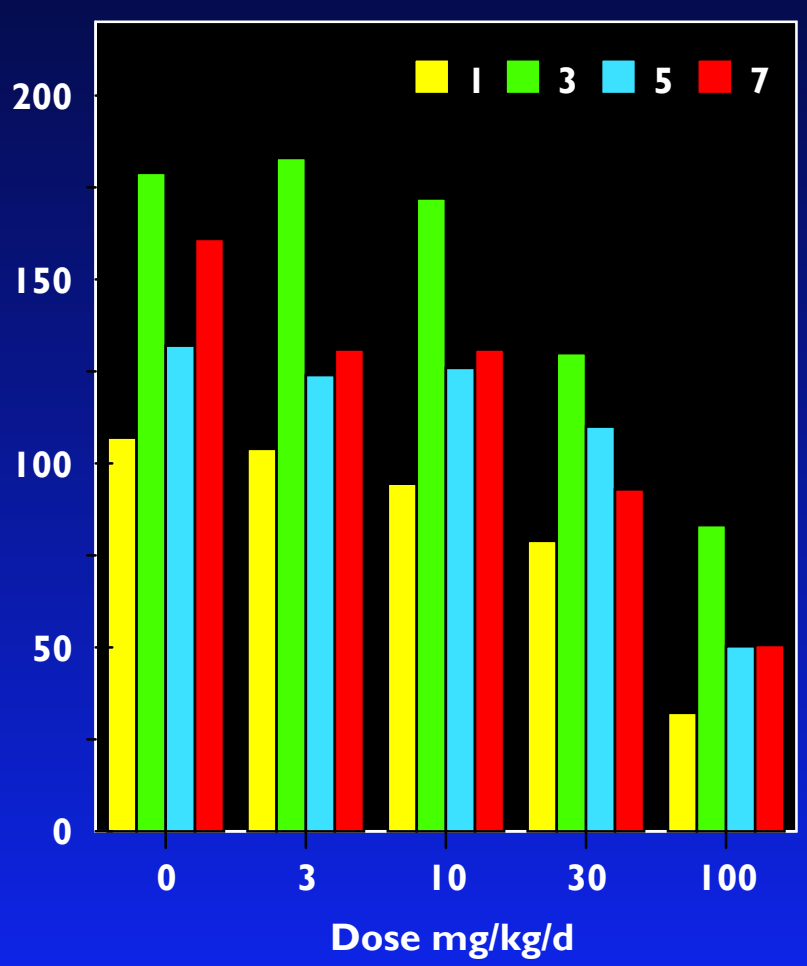
VINCLOZOLIN data

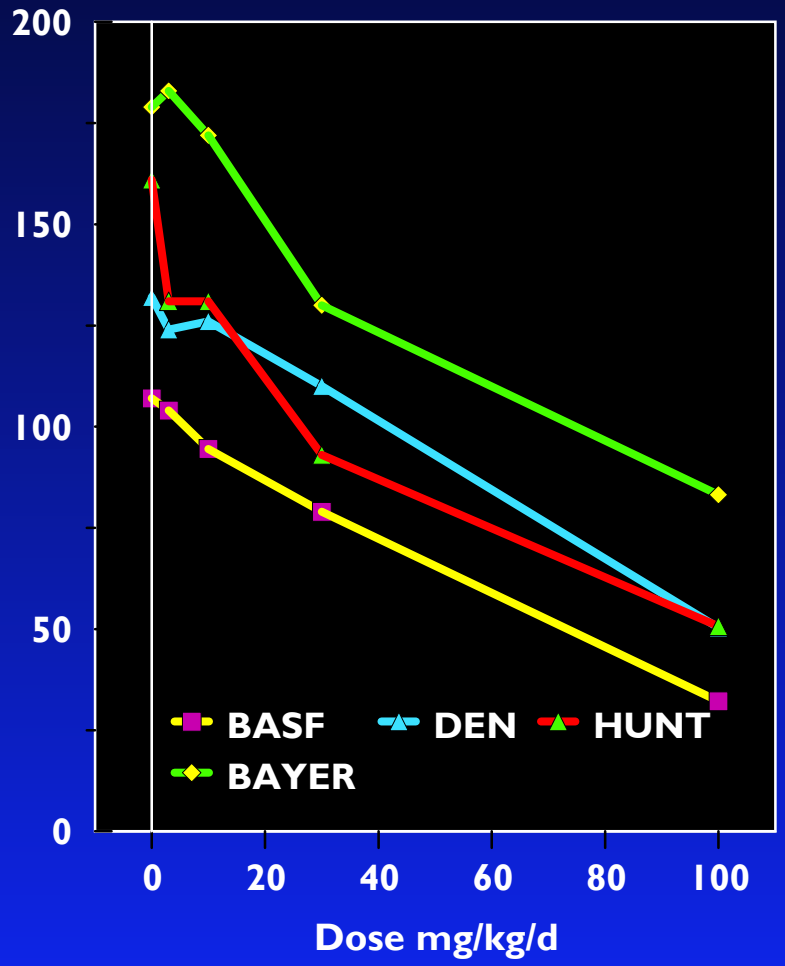
41. Effect of VINCLOZOLIN on Ventral Prostate weights. Data from four labs



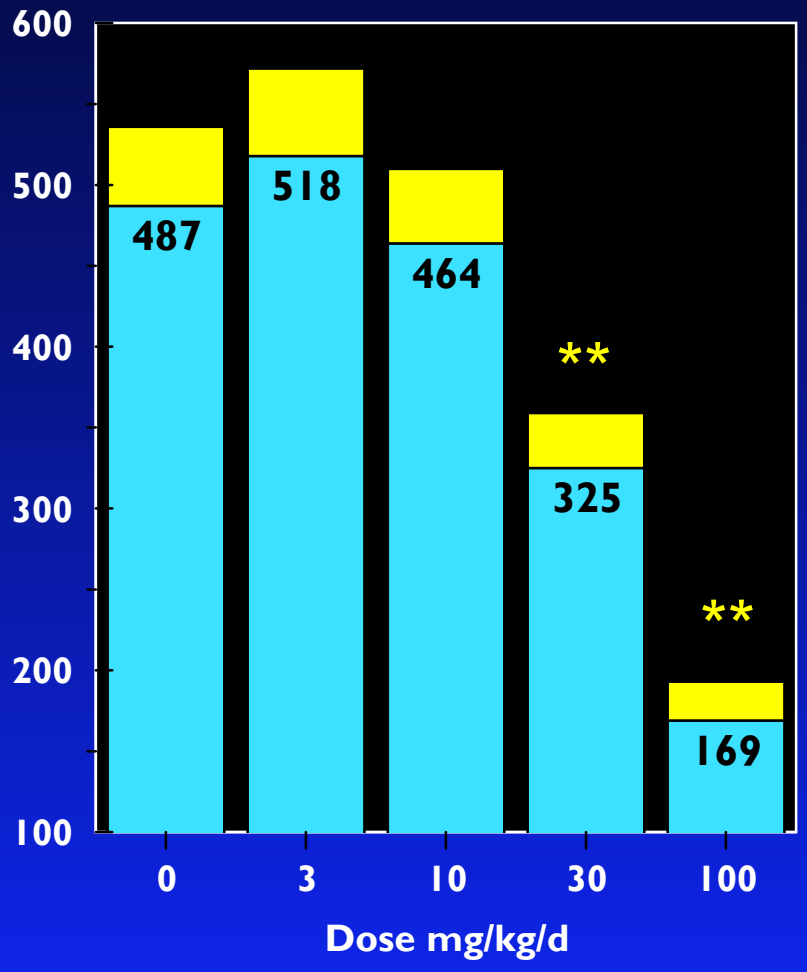


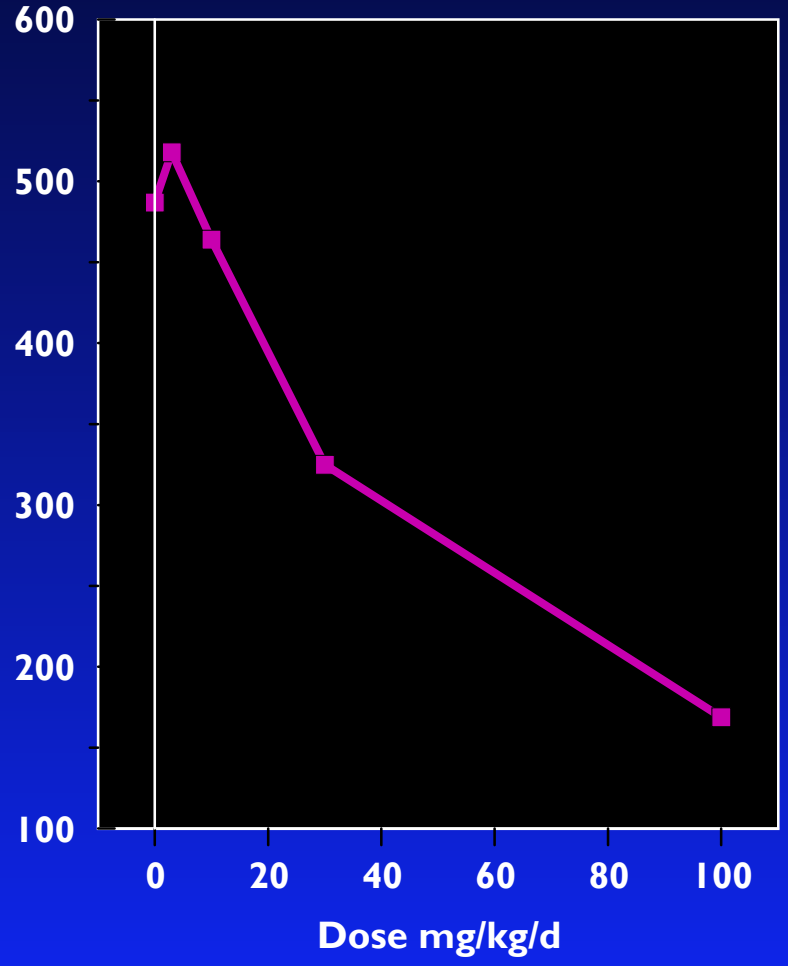
42. Effect of Vinclozolin on VP weights. Data from four labs



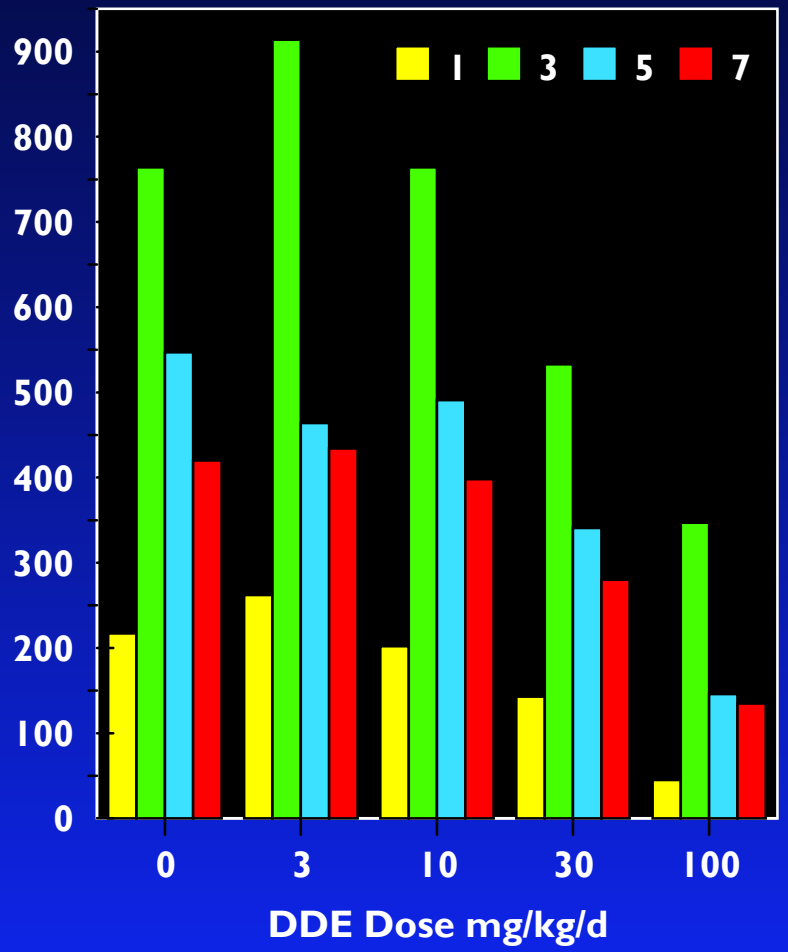


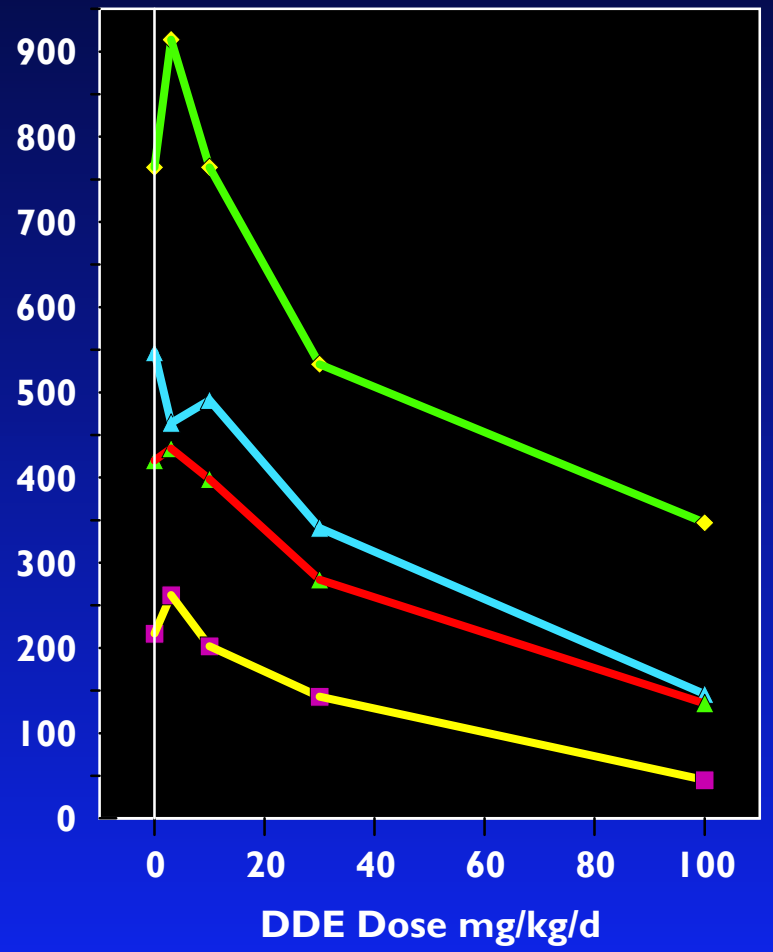
43. Effect of VINCLOZOLIN on Seminal Vesicle weights. Data from four labs



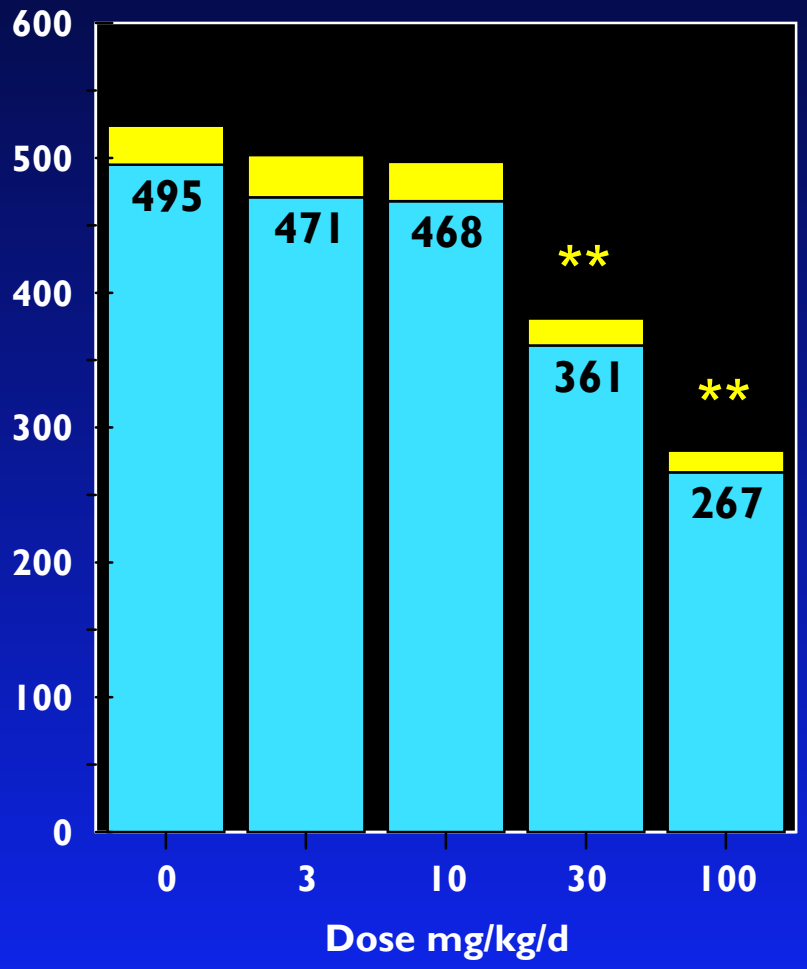


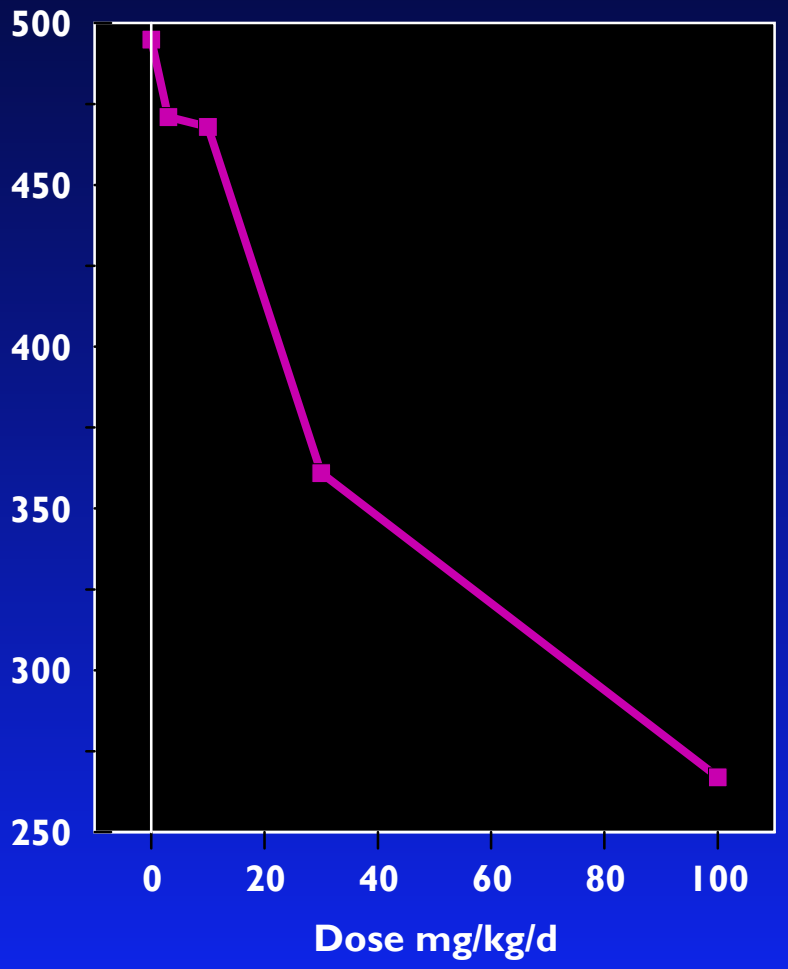
44. Effect of vinclozolin on Seminal Vesicle weights. Data from four labs



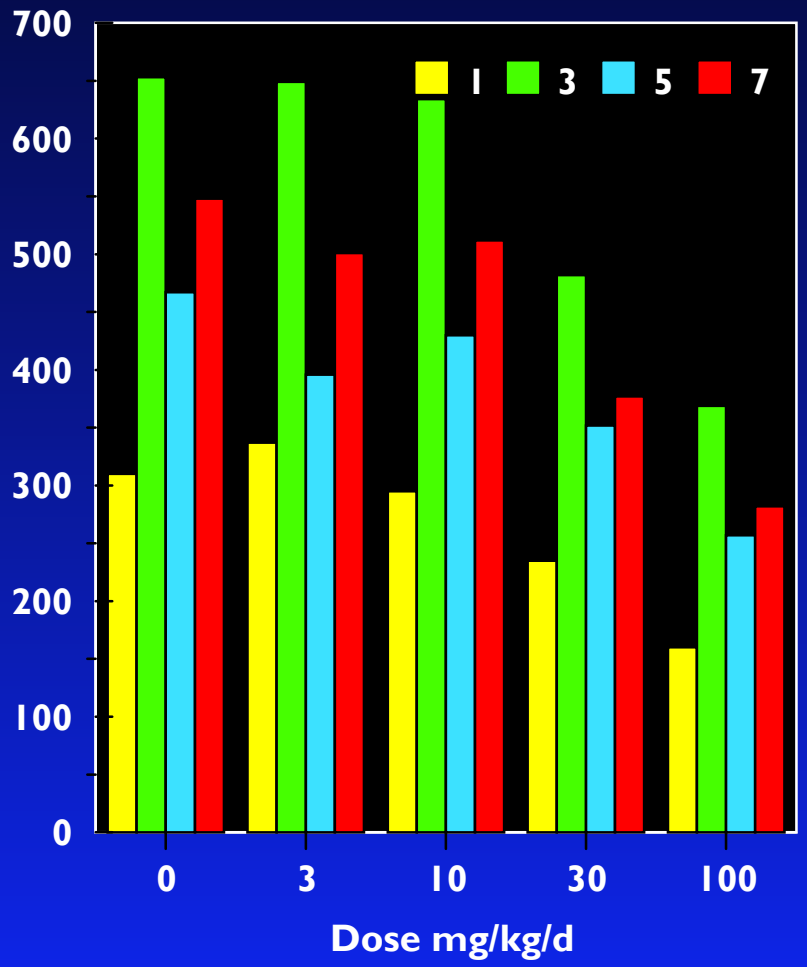


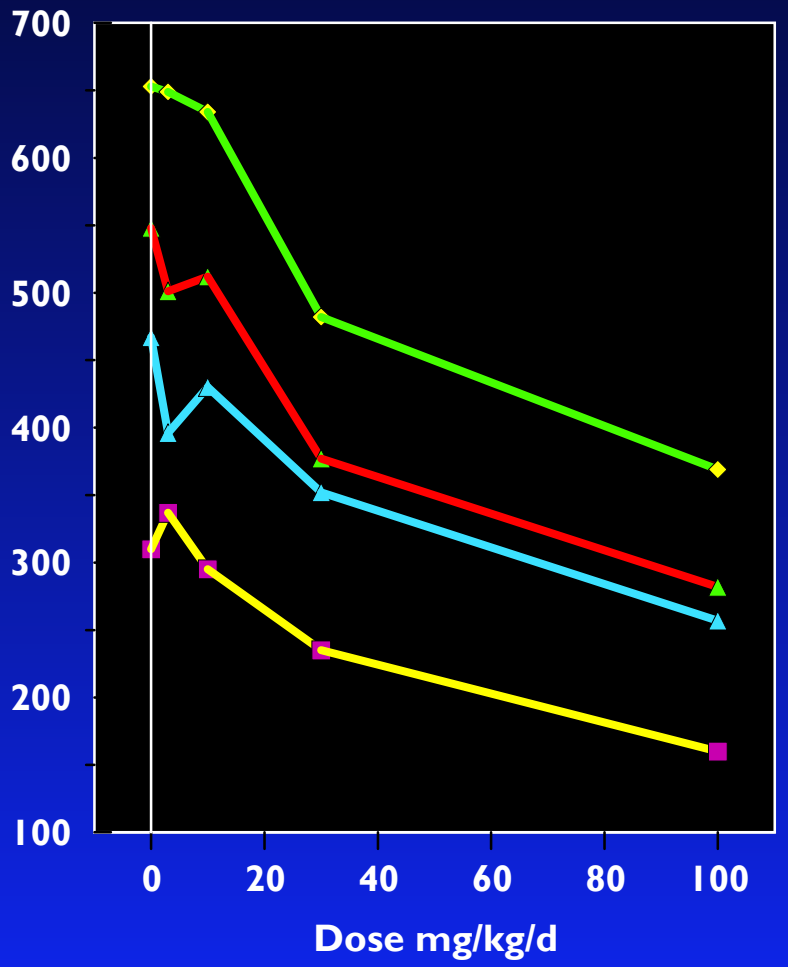
45. Effect of VINCLOZOLIN on LABC weights. Data from four labs



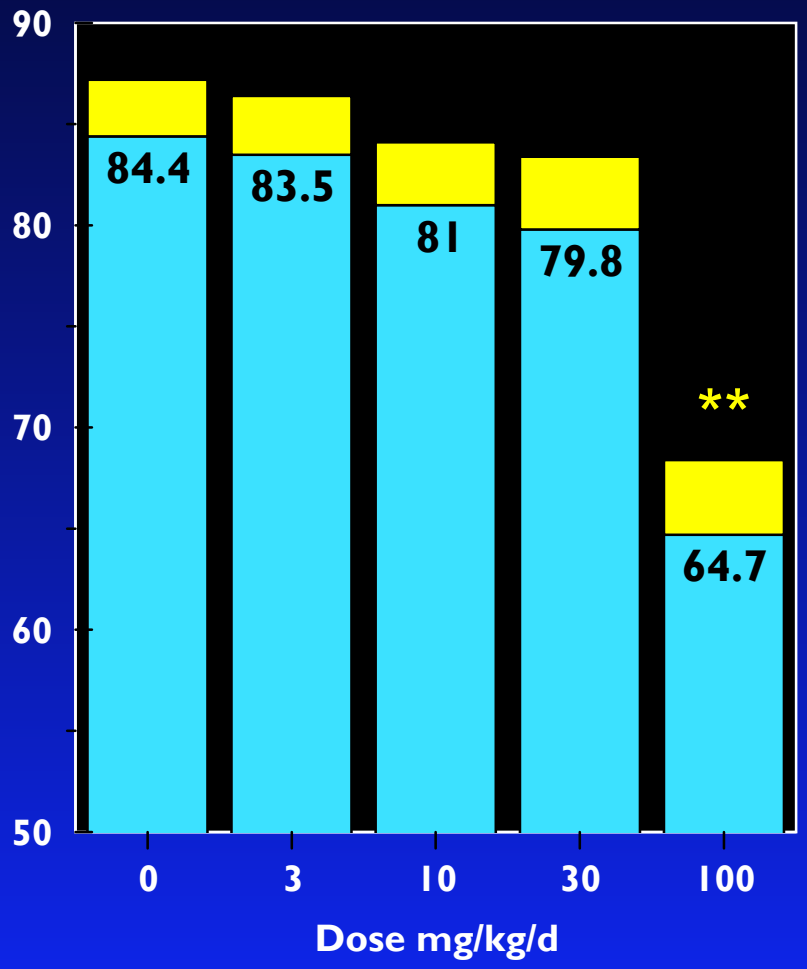


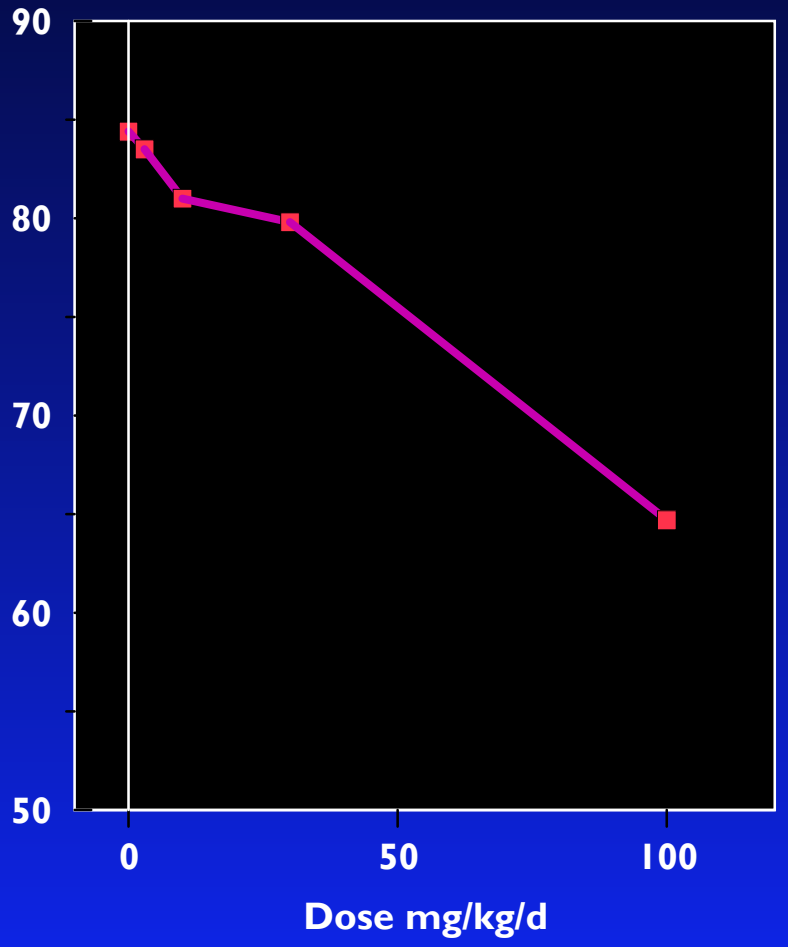
46. Effect of VINCLOZOLIN on LABC weights. Data from four labs



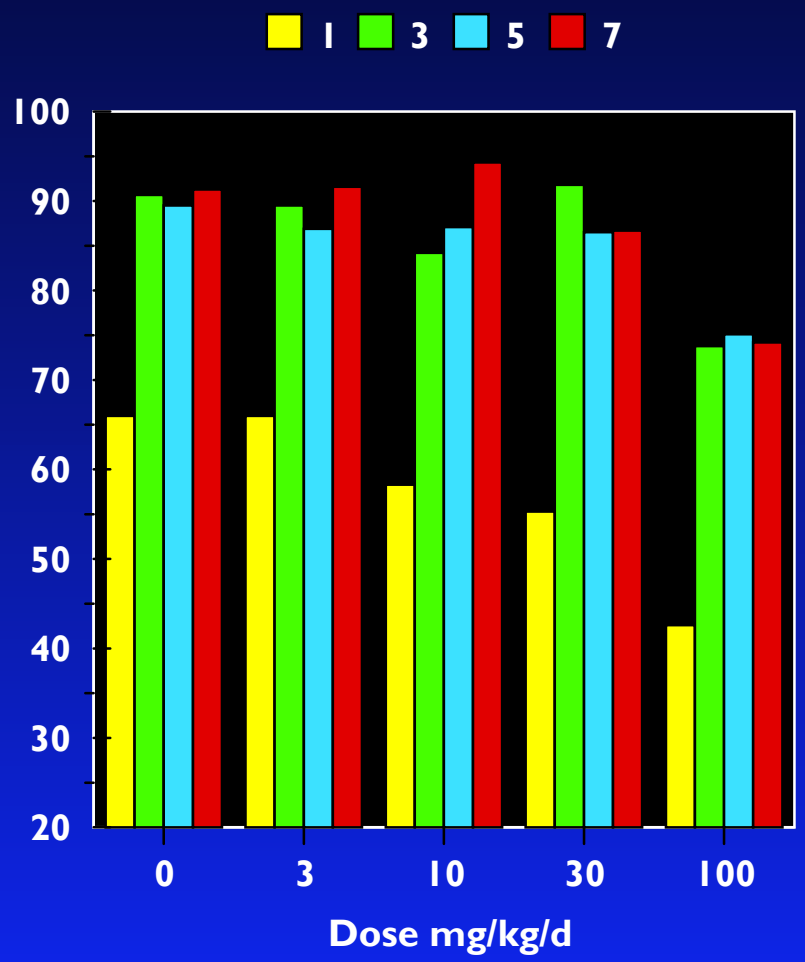


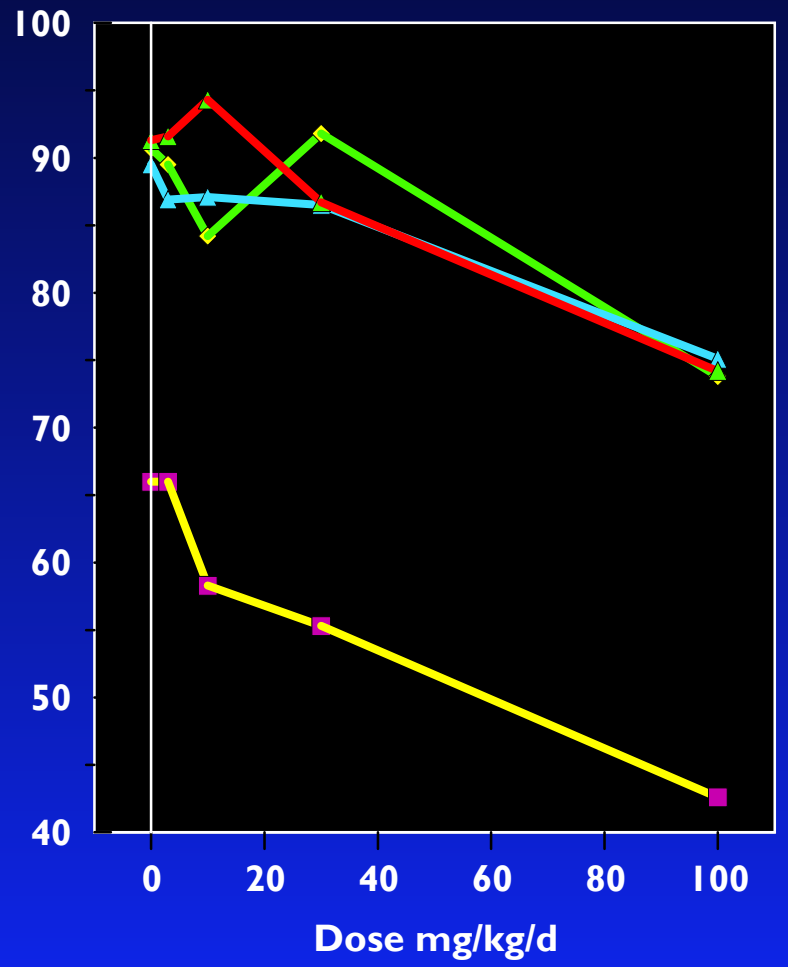
47. Effect of VINCLOZOLIN on Glans penis weights. Data from four labs



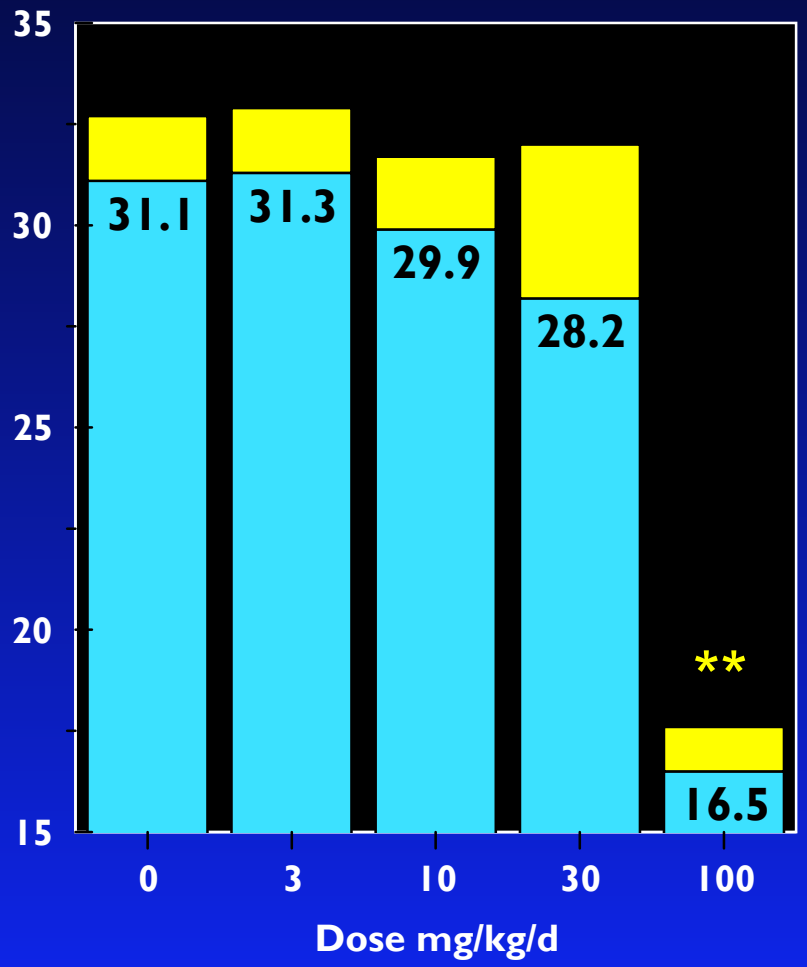


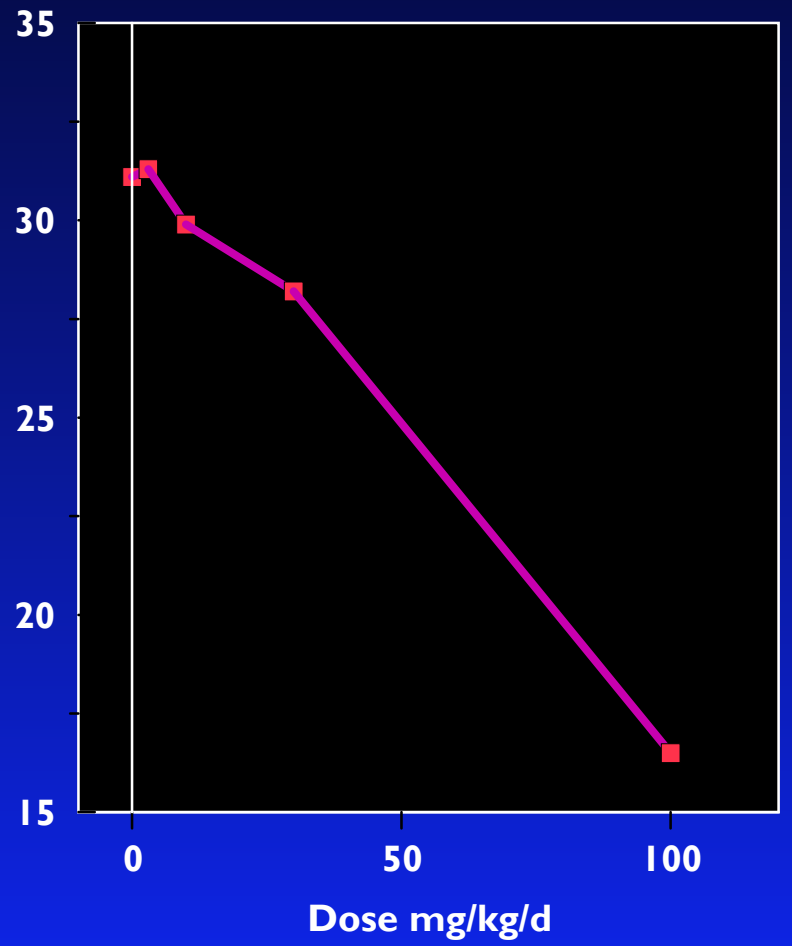
48. Effect of Vinclozolin on Glans Penis weights. Data from four labs



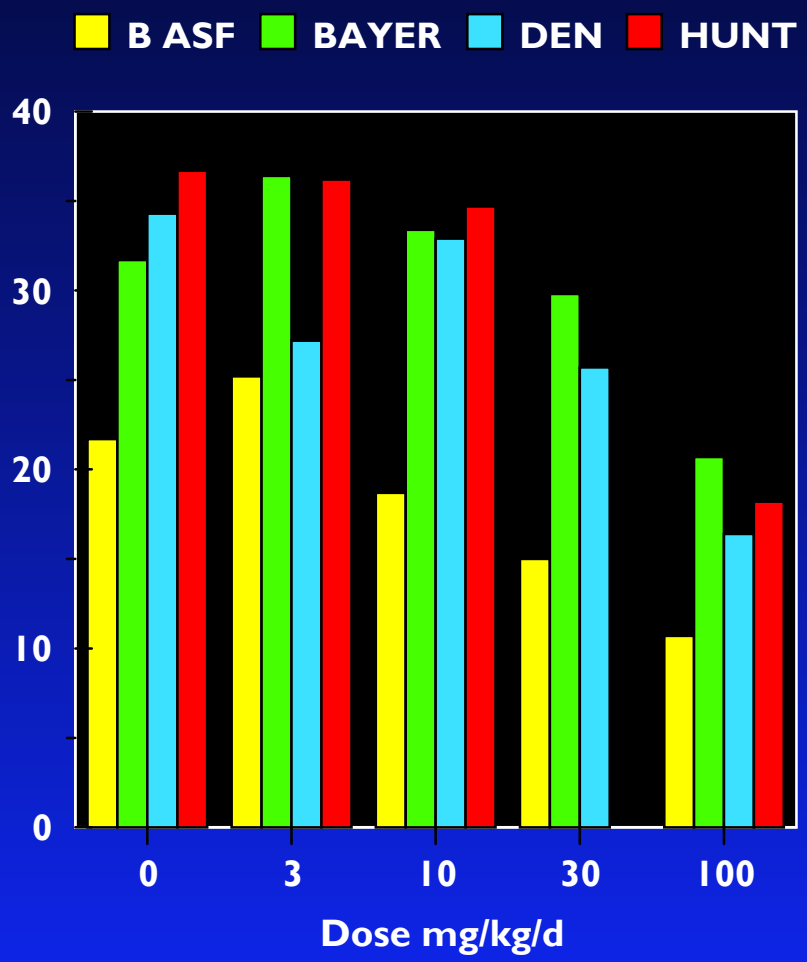


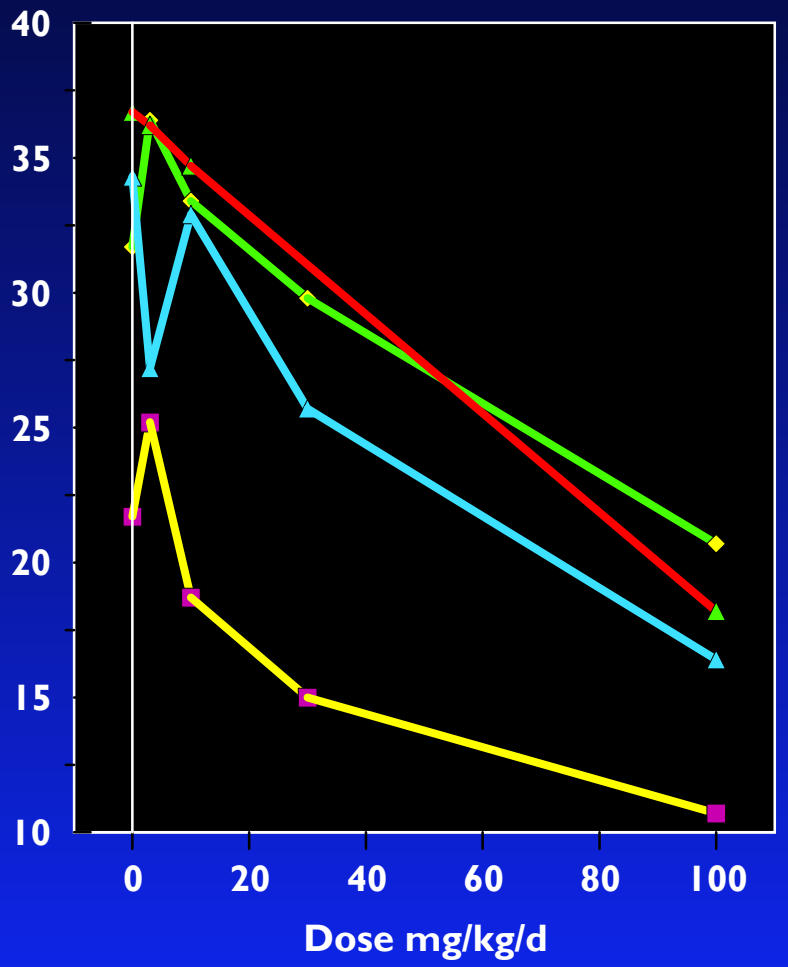
49. Effect of VINCLOZOLIN on Cowper's gland weights. Data from four labs



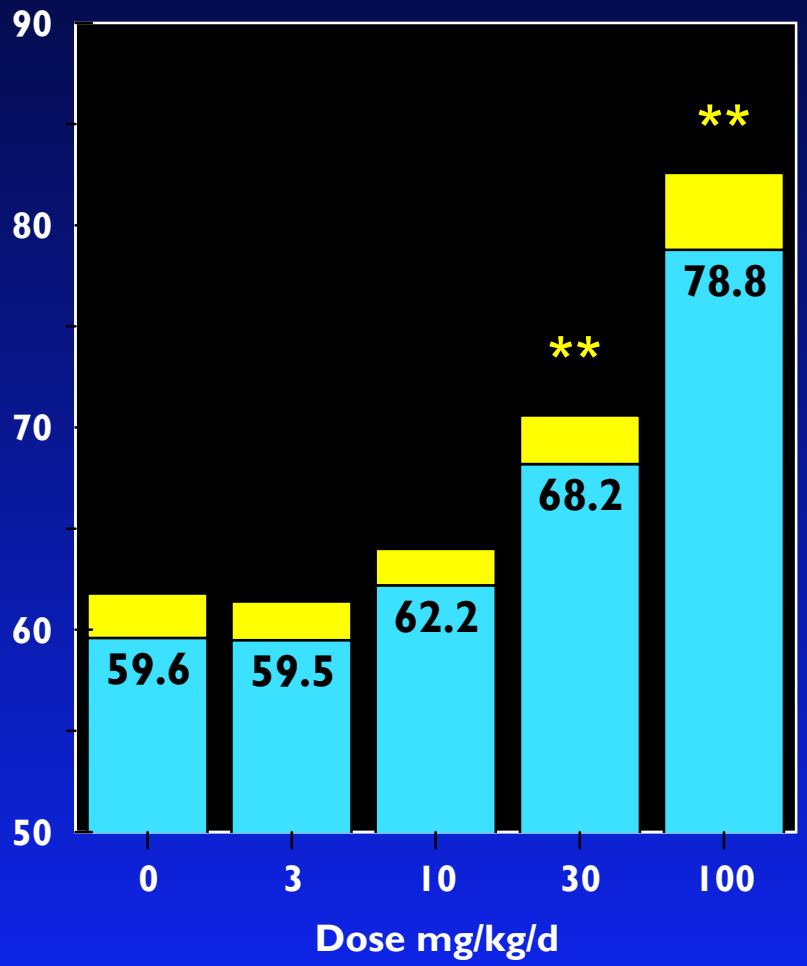


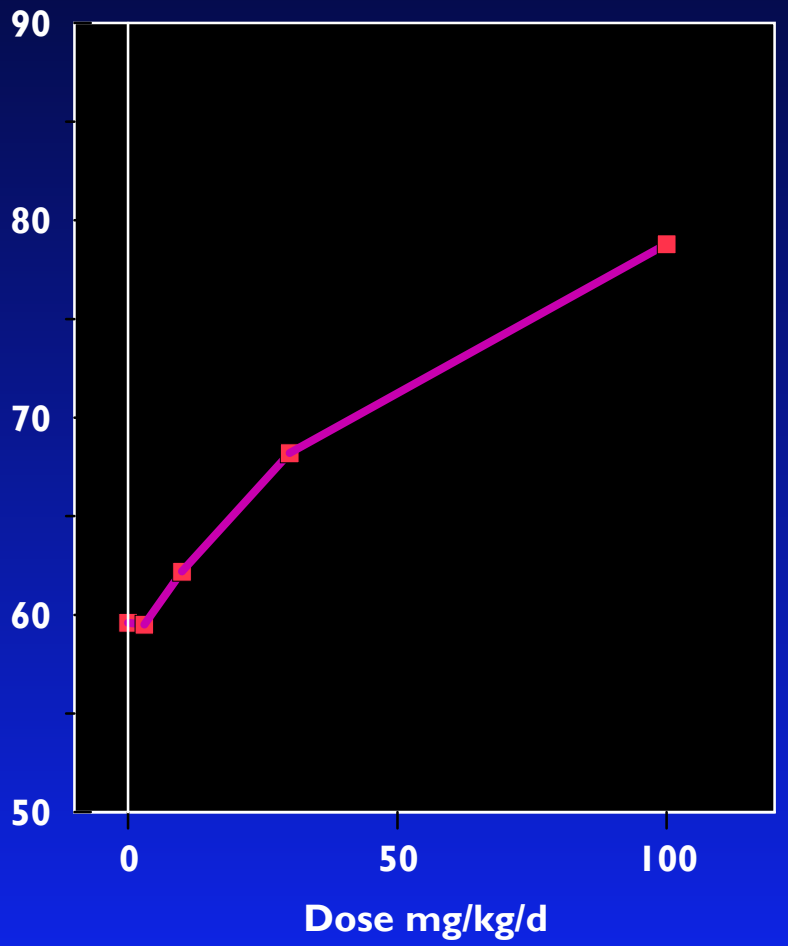
50.Effect of Vinclozolin on Cowper's gland weights. Data from four labs



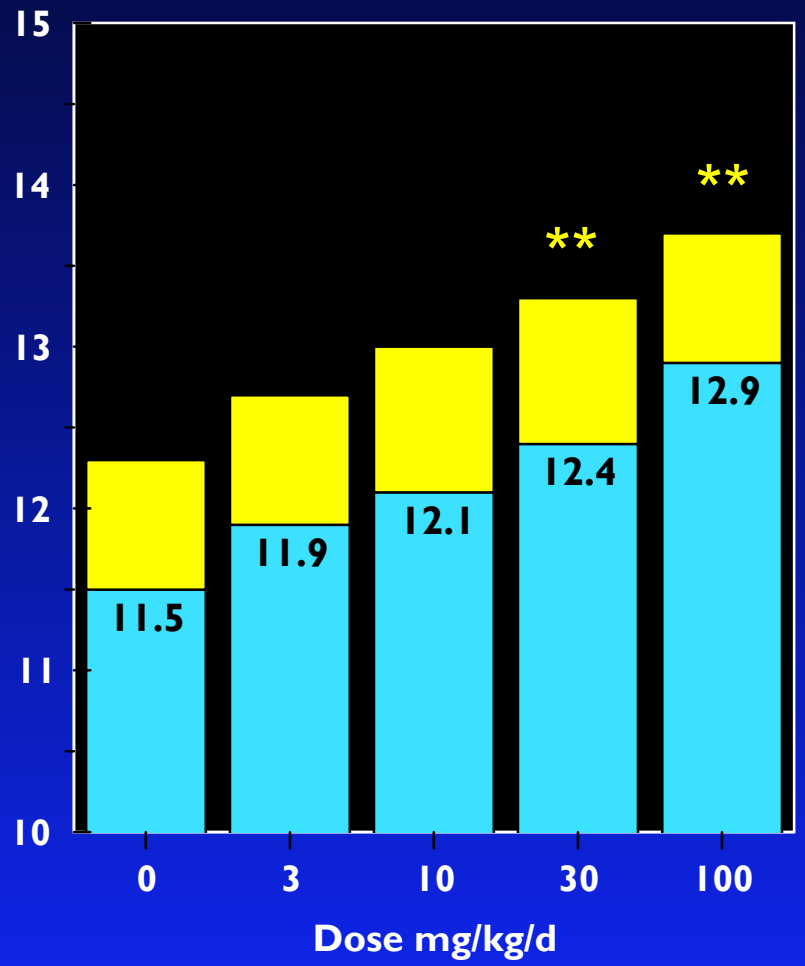


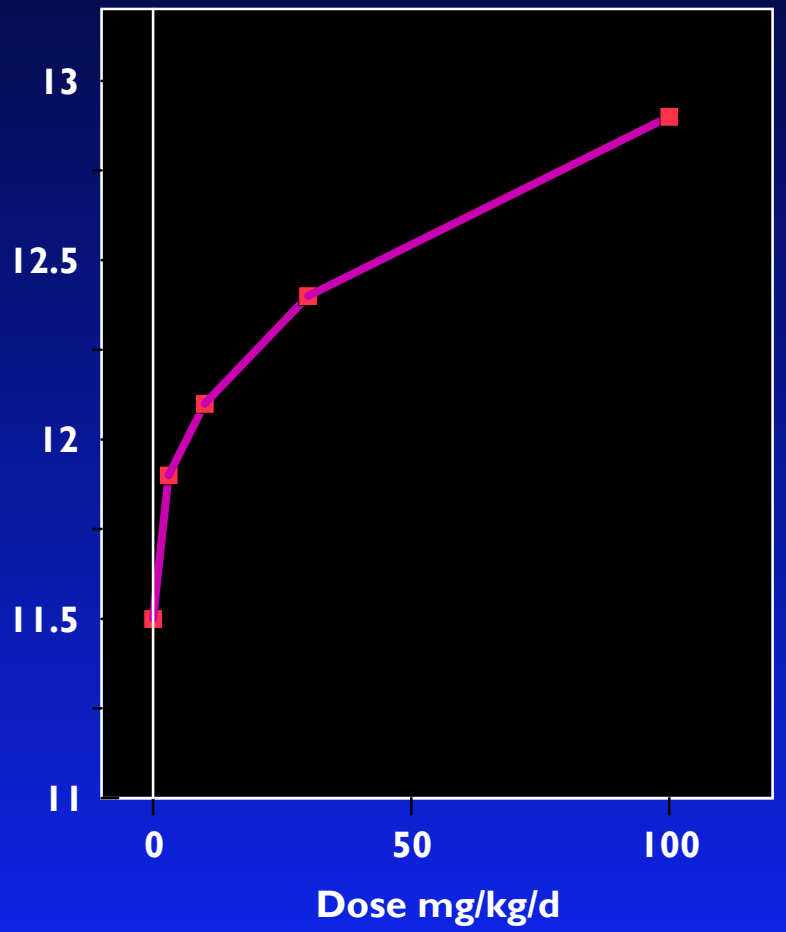
51.Effect of VINCLOZOLIN on Adrenal weights. Data from four labs



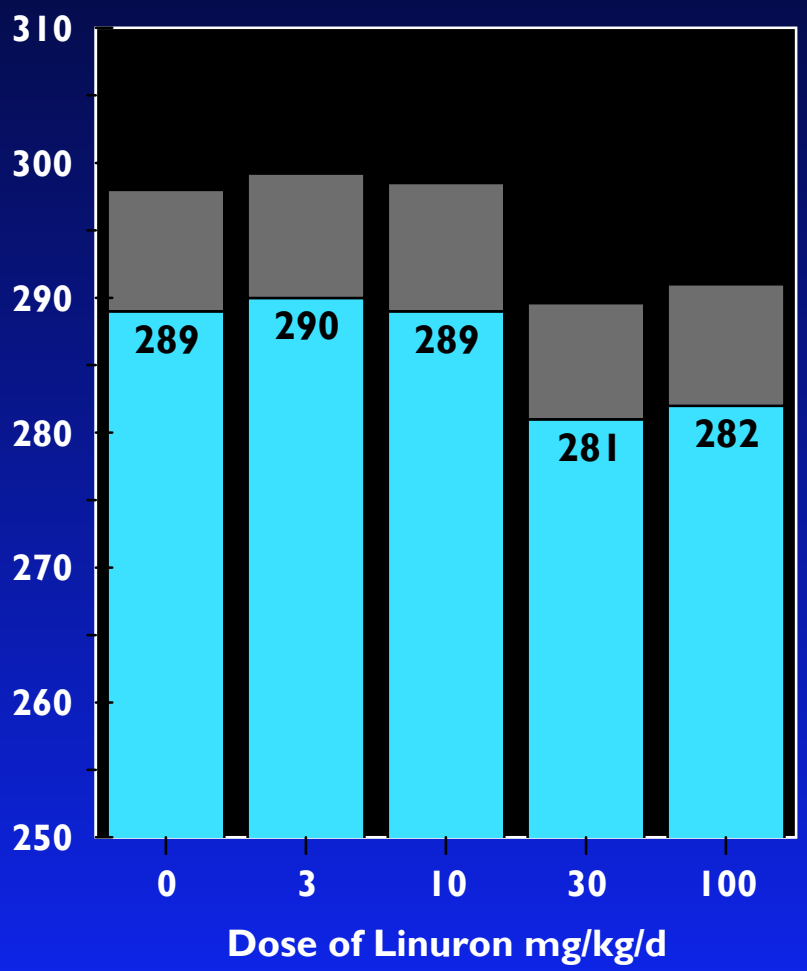


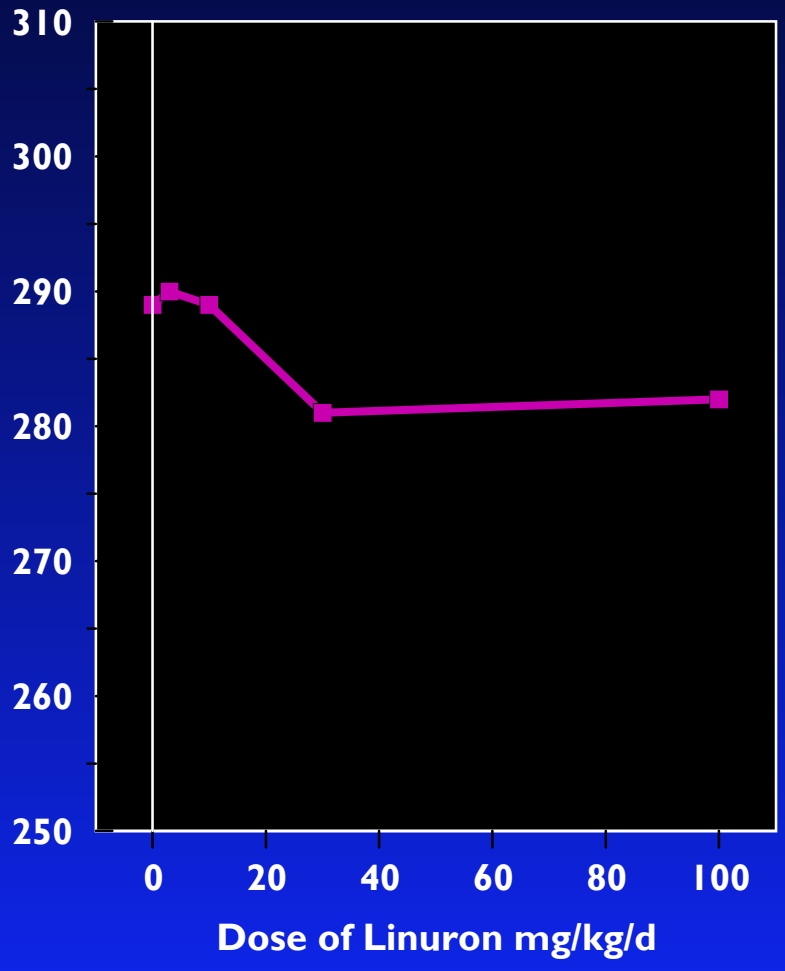
52.Effect of VINCLOZOLIN on Liver weights. Data from four labs





53. Effects of VINCLOZOLIN on Body weight at necropsy - 4 LABS





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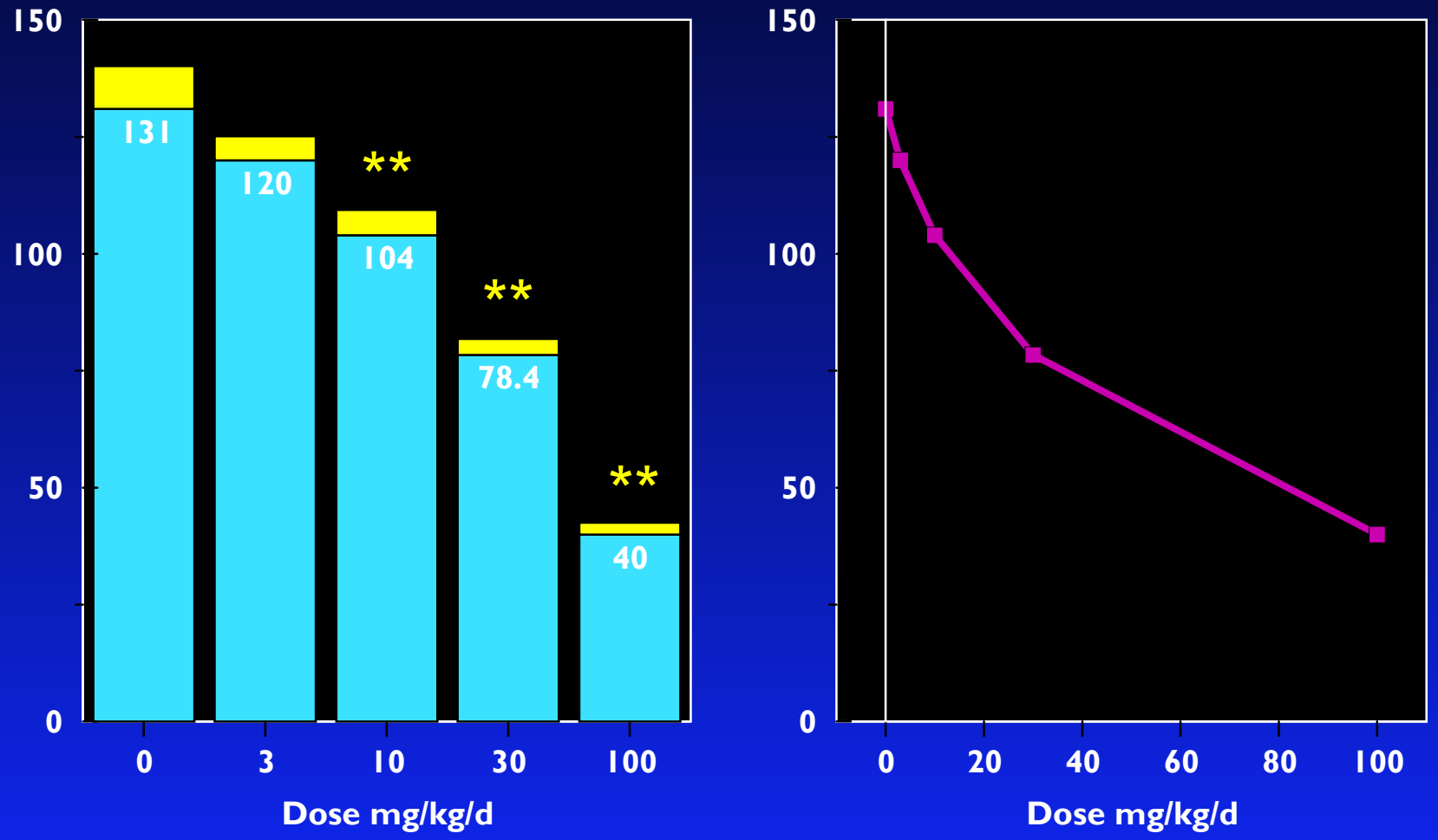
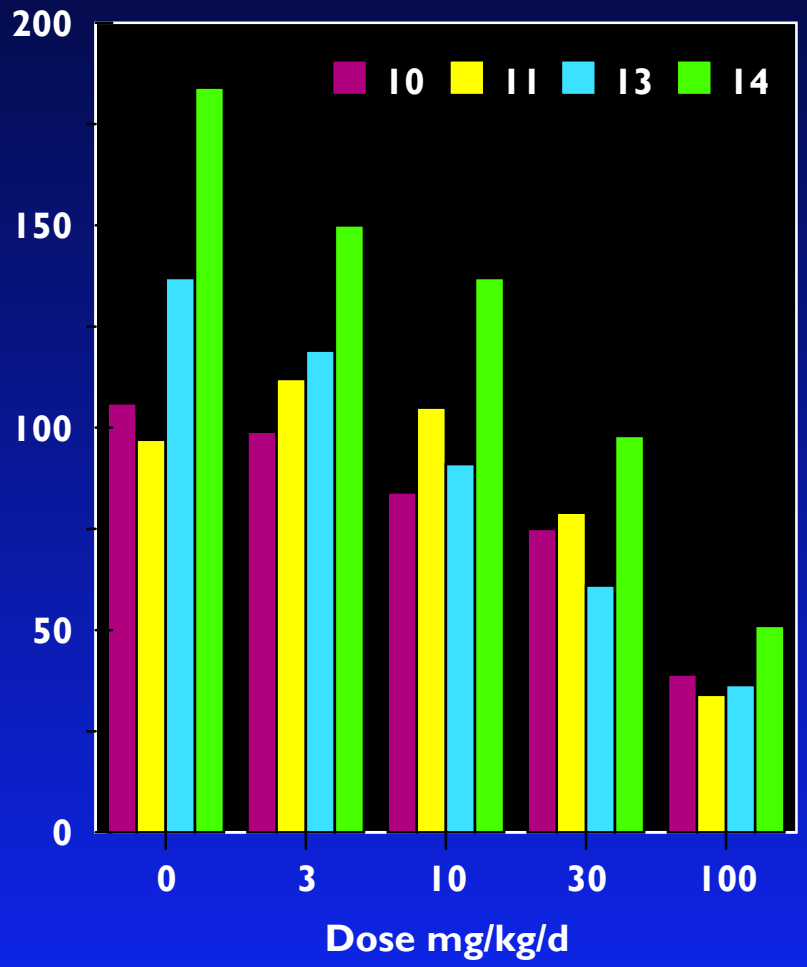
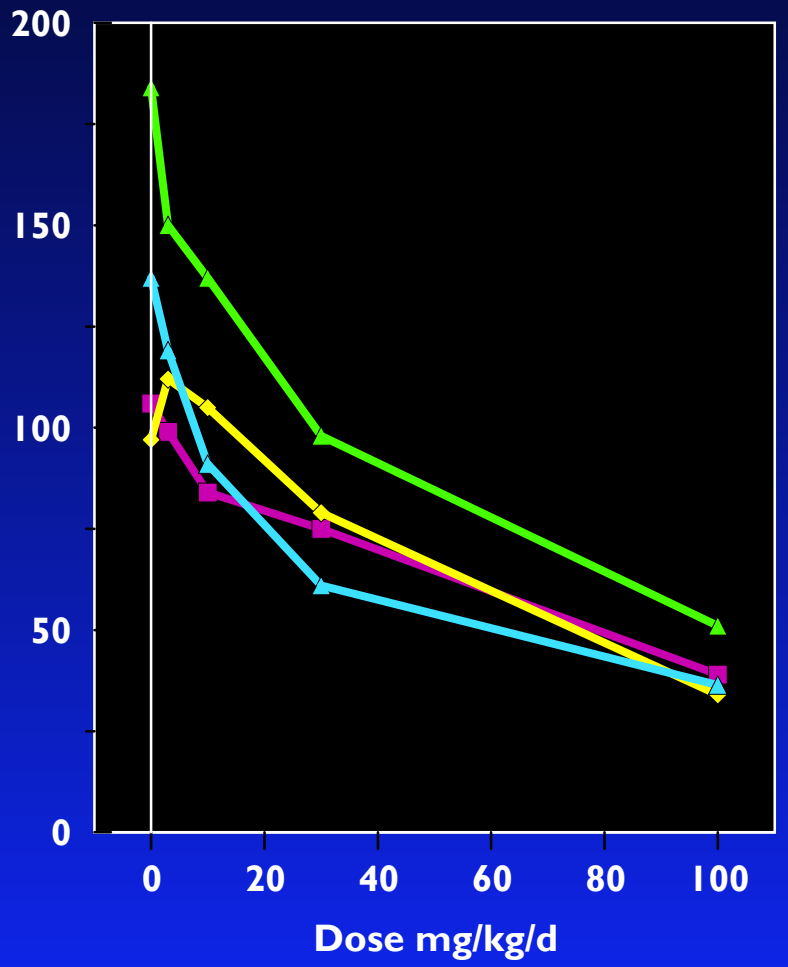
54. Effect of vinclozolin on ventral prostate weights. Data from four labs

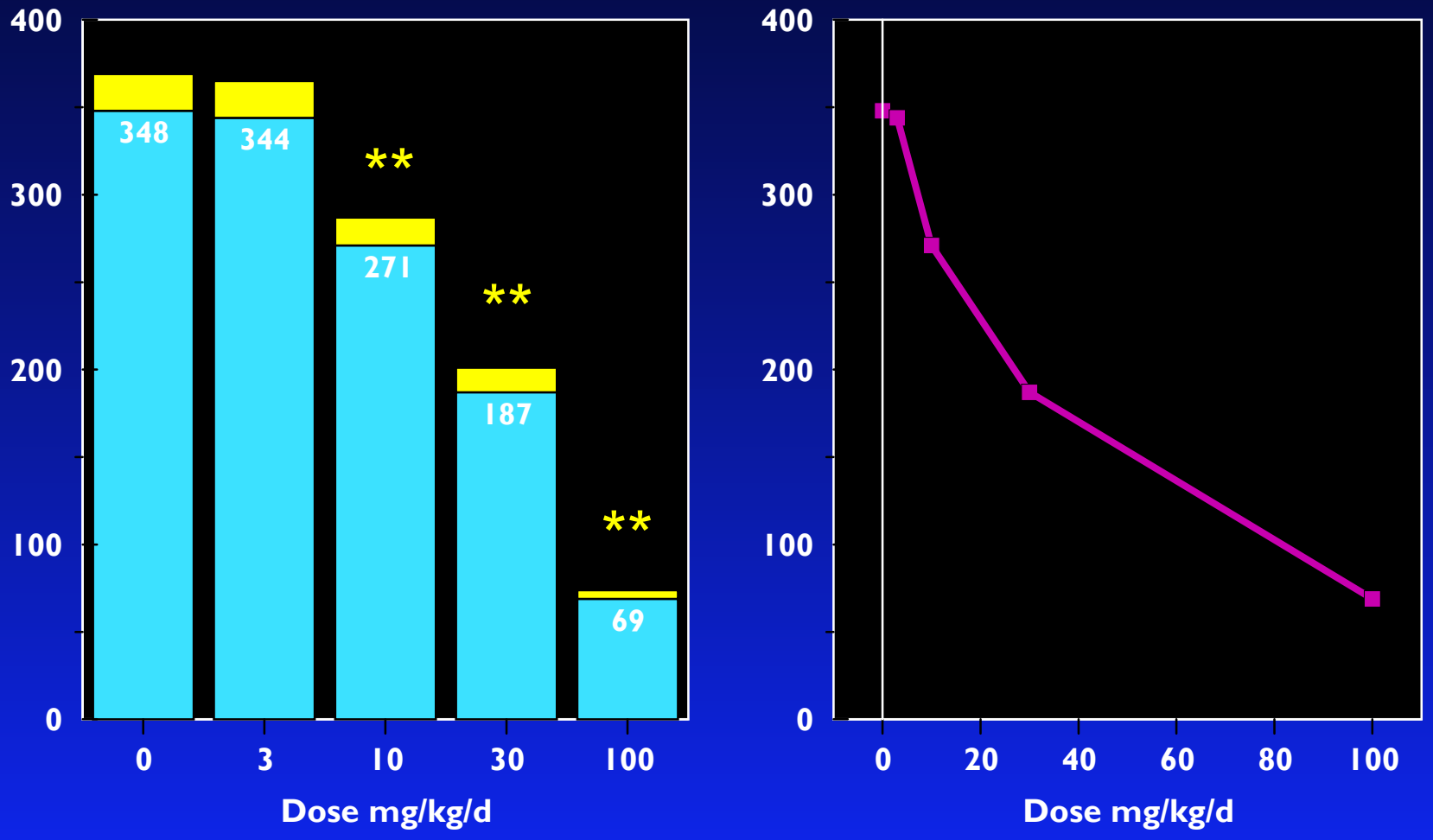


55. Effect of vinclozolin on ventral prostate weights. Data from four labs

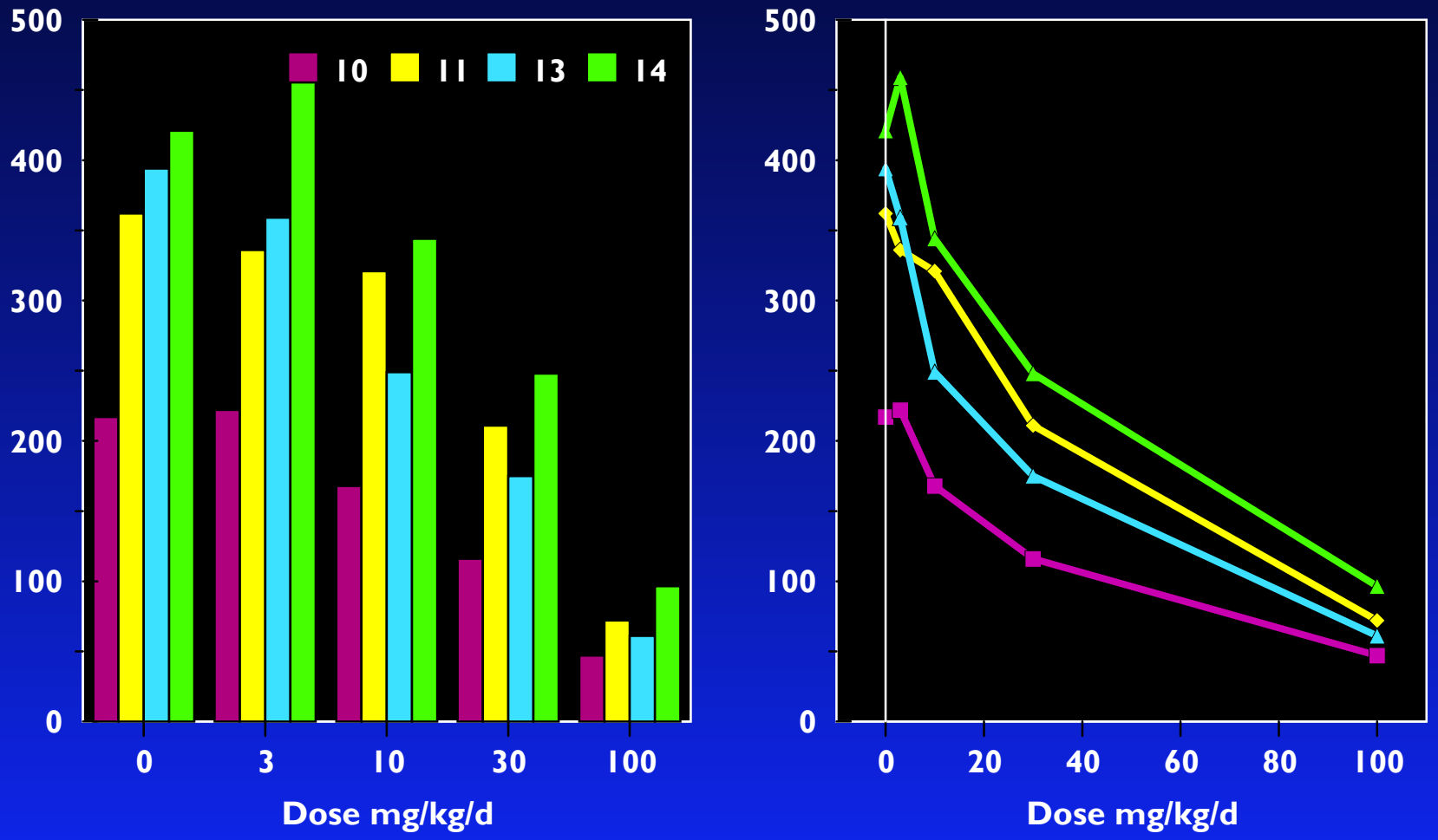




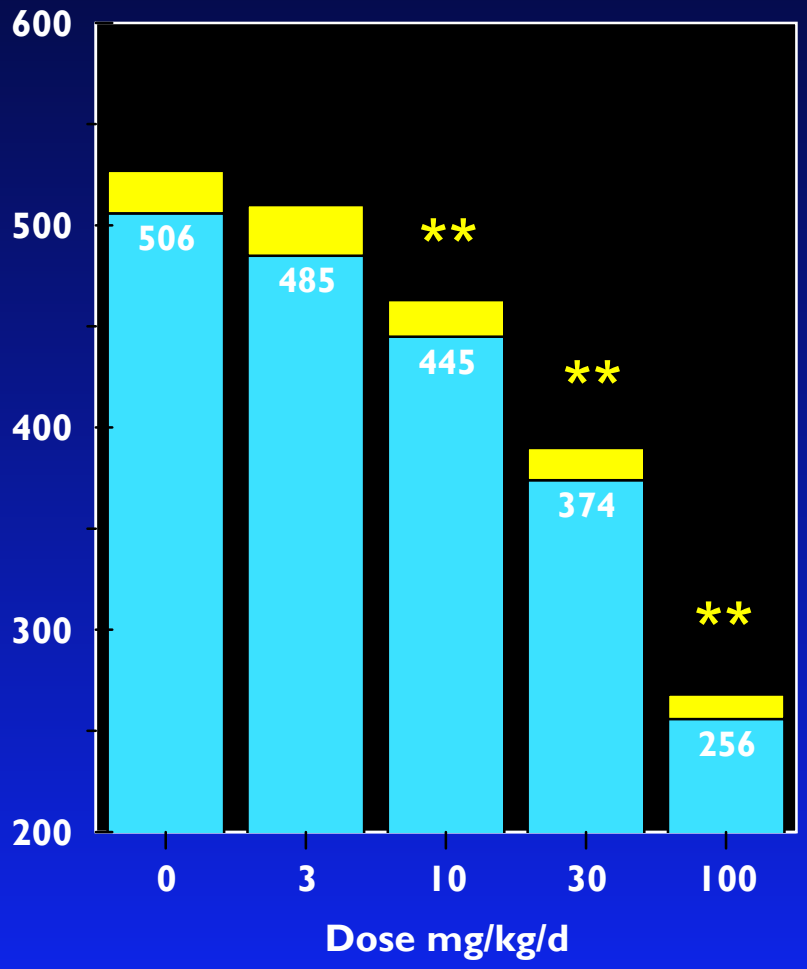
56. Effect of vinclozolin on seminal vesicle weights. Data from four labs

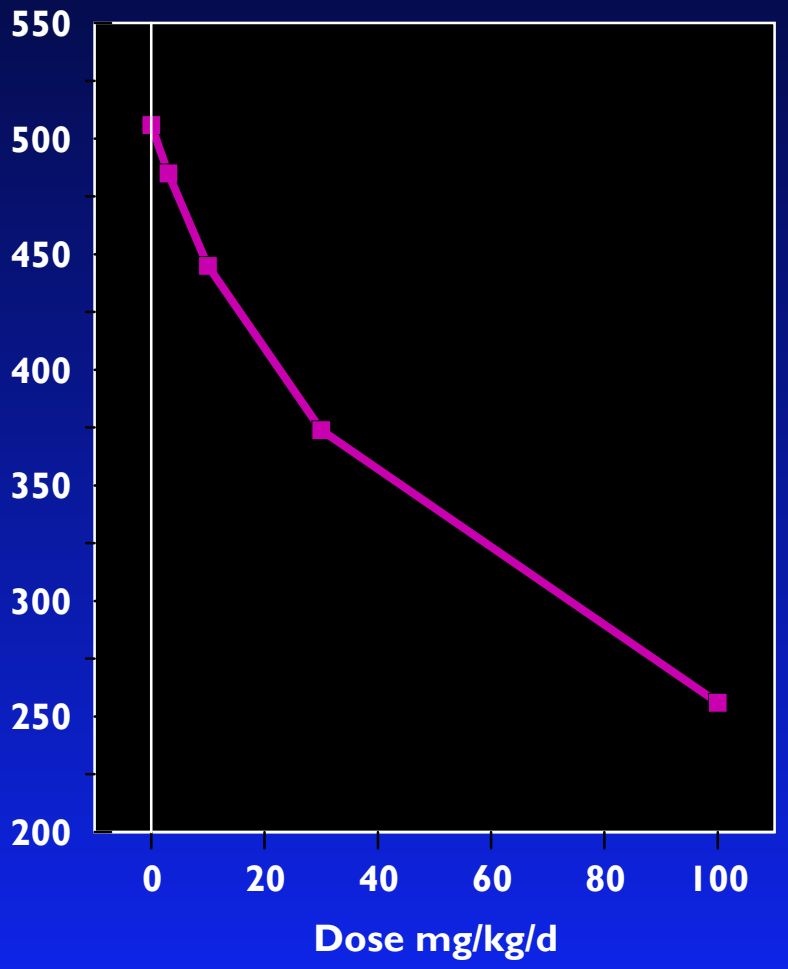


57. Effect of vinclozolin on seminal vesicle weights. Data from four labs

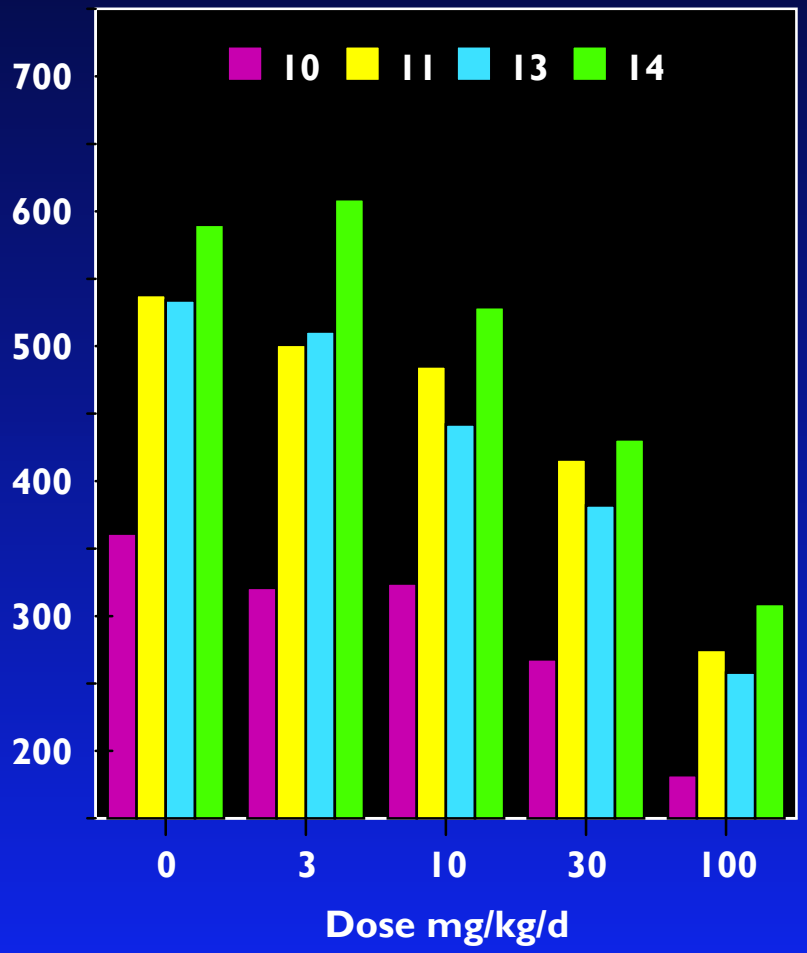


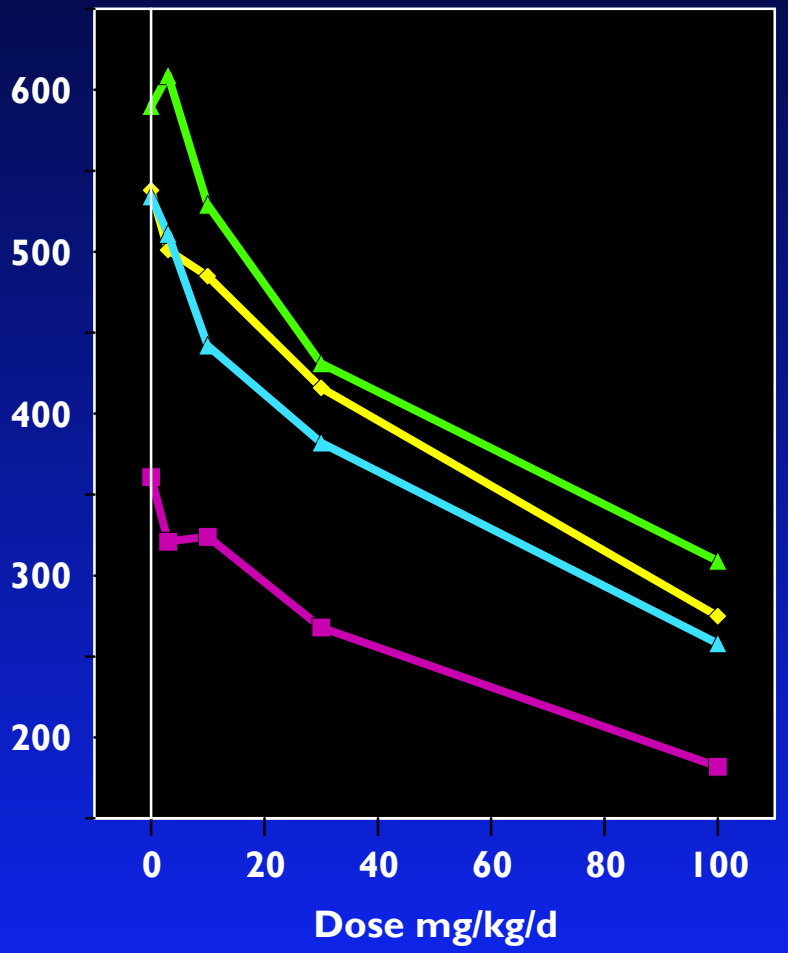
58. Effect of vinclozolin on LABC weights. Data from four labs



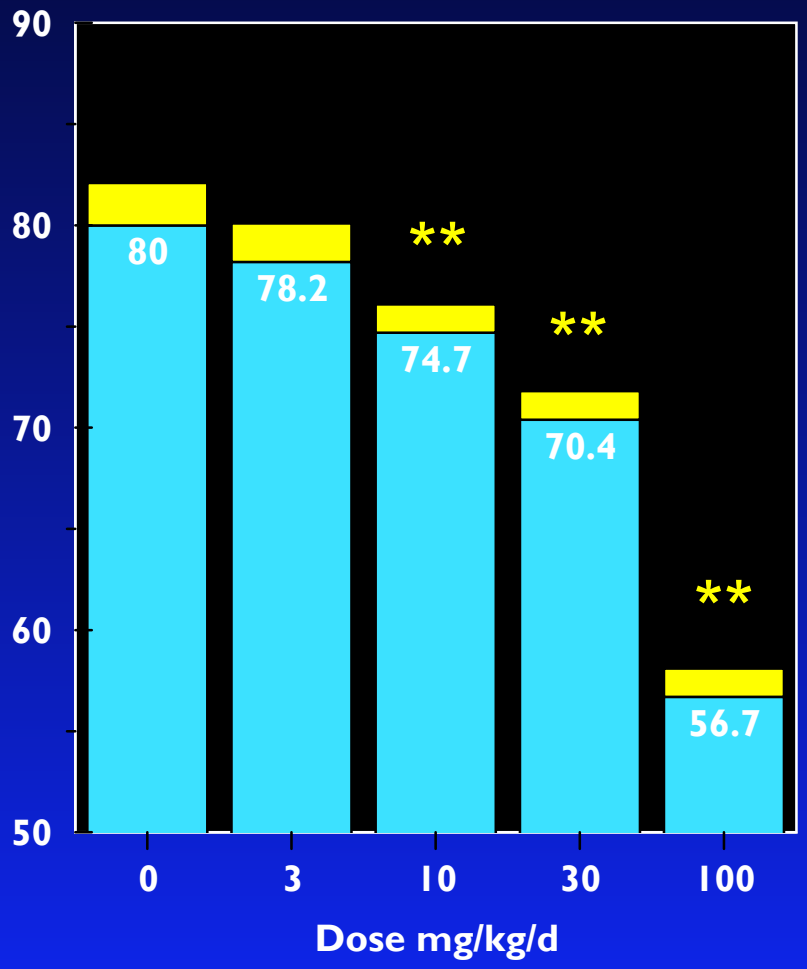


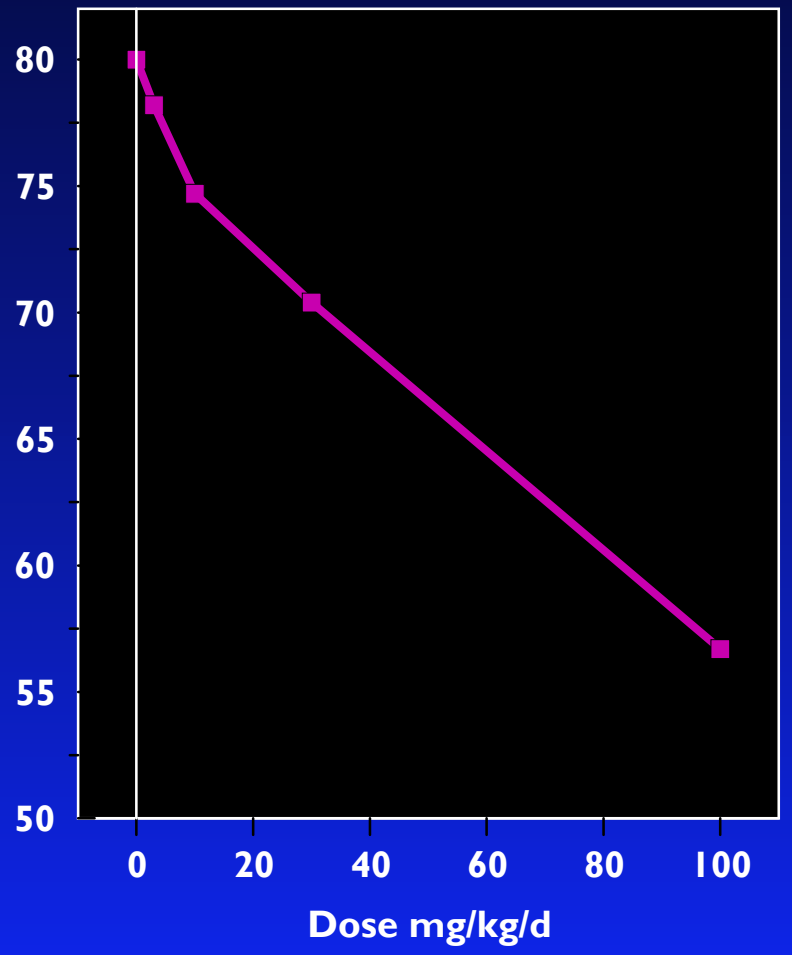
59. Effect of vinclozolin on LABC weights. Data from four labs



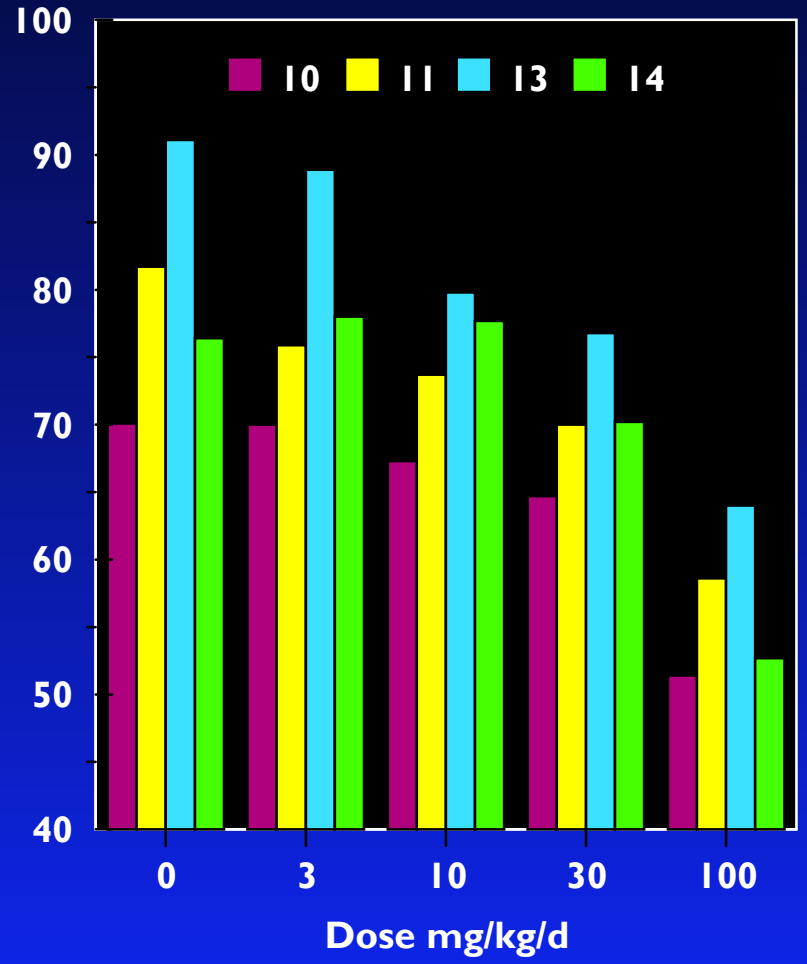


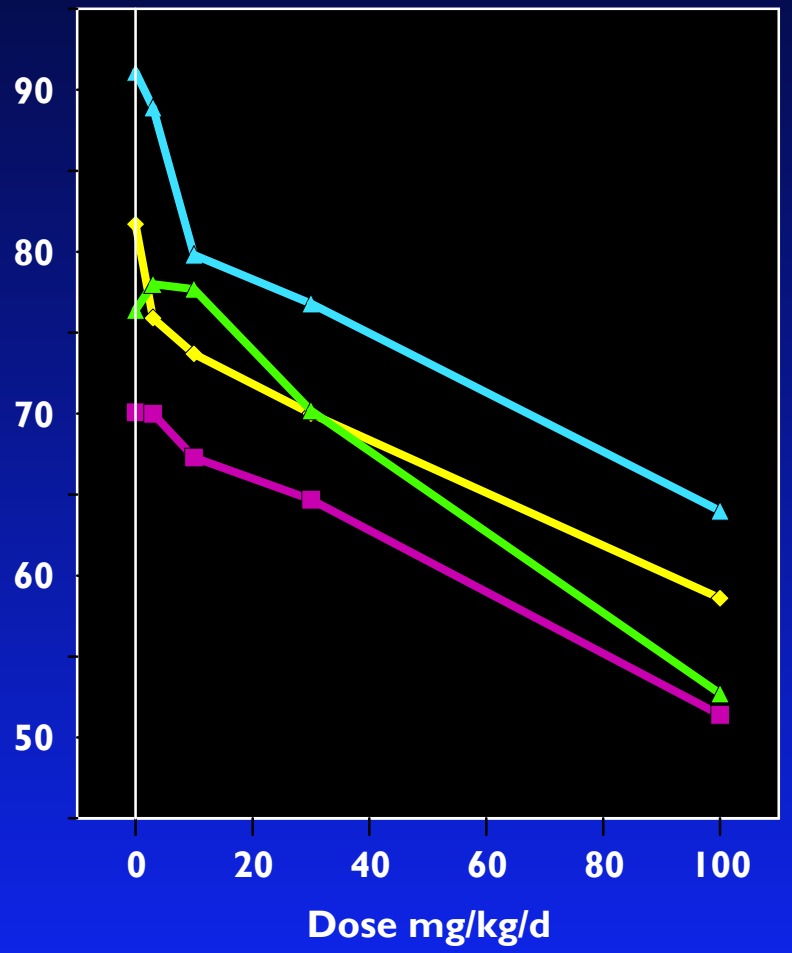
60. Effect of vinclozolin on glans penis weights. Data from four labs



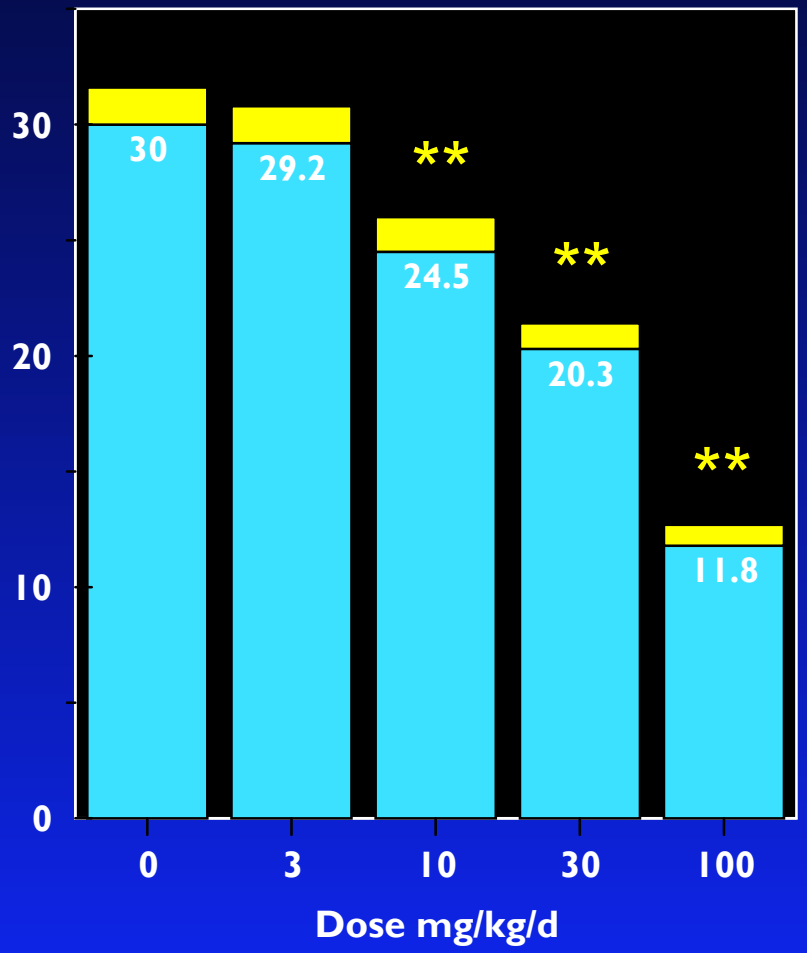


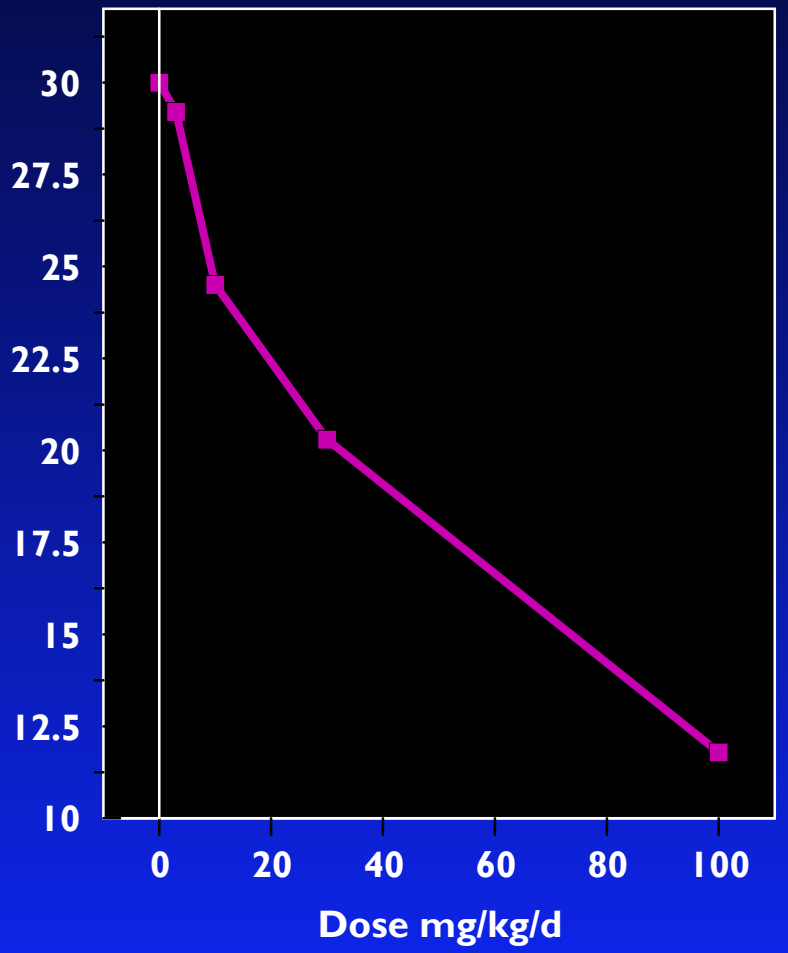
61. Effect of vinclozolin on Glans Penis weights. Data from four labs



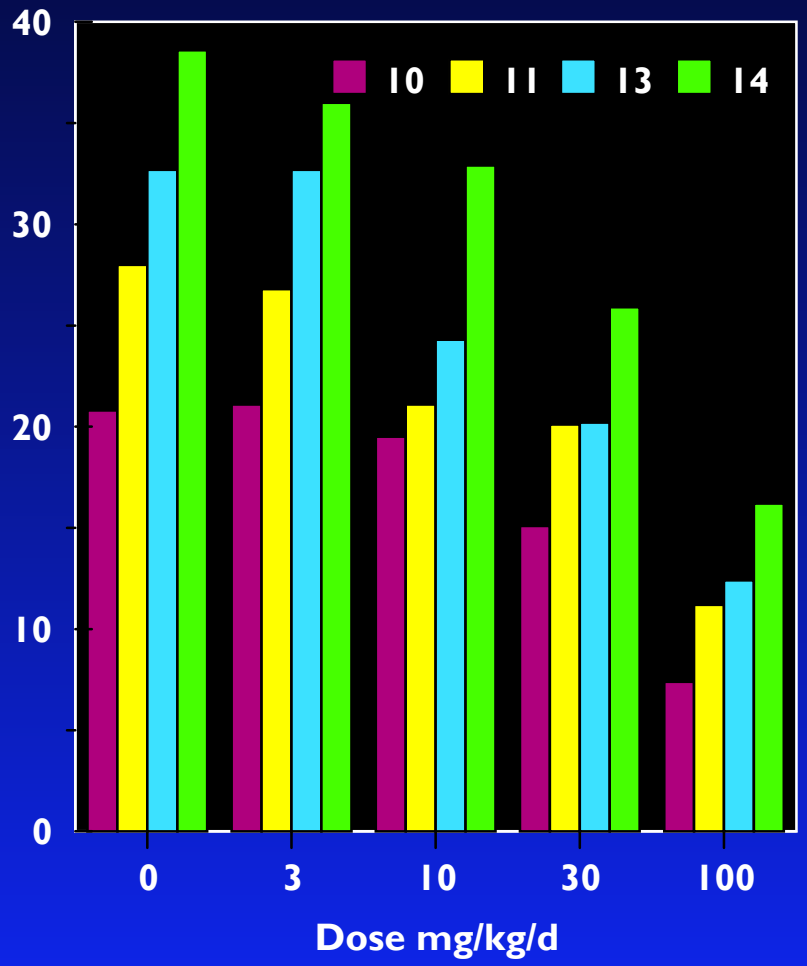


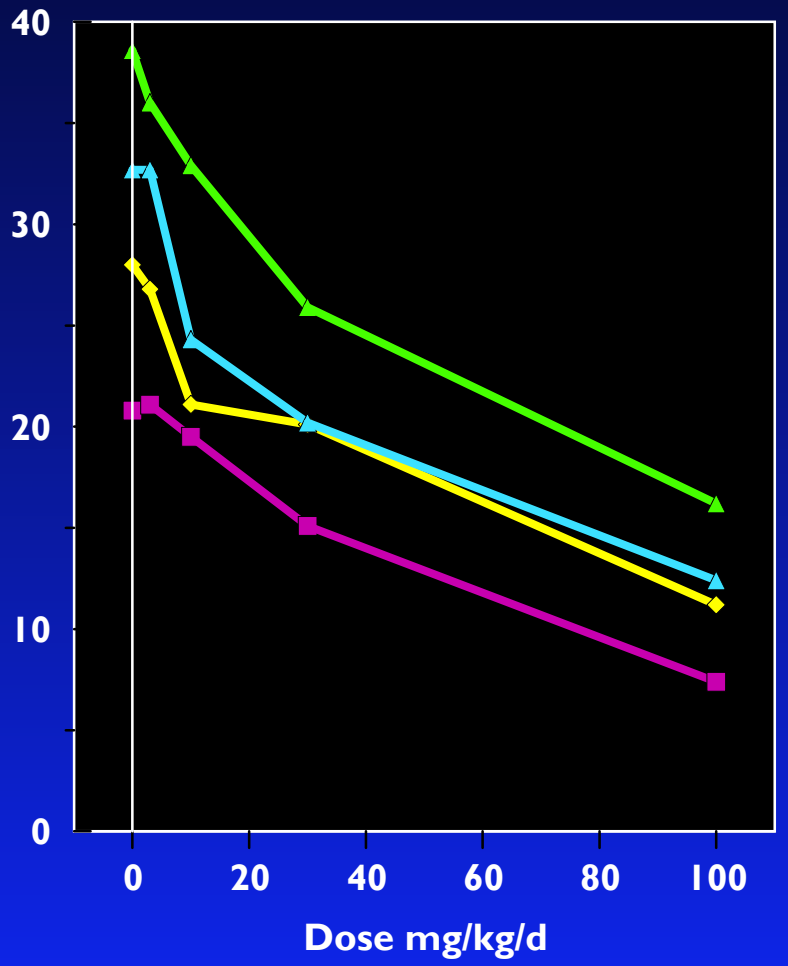
62. Effect of vinclozolin on Cowper's gland weights. Data from four labs



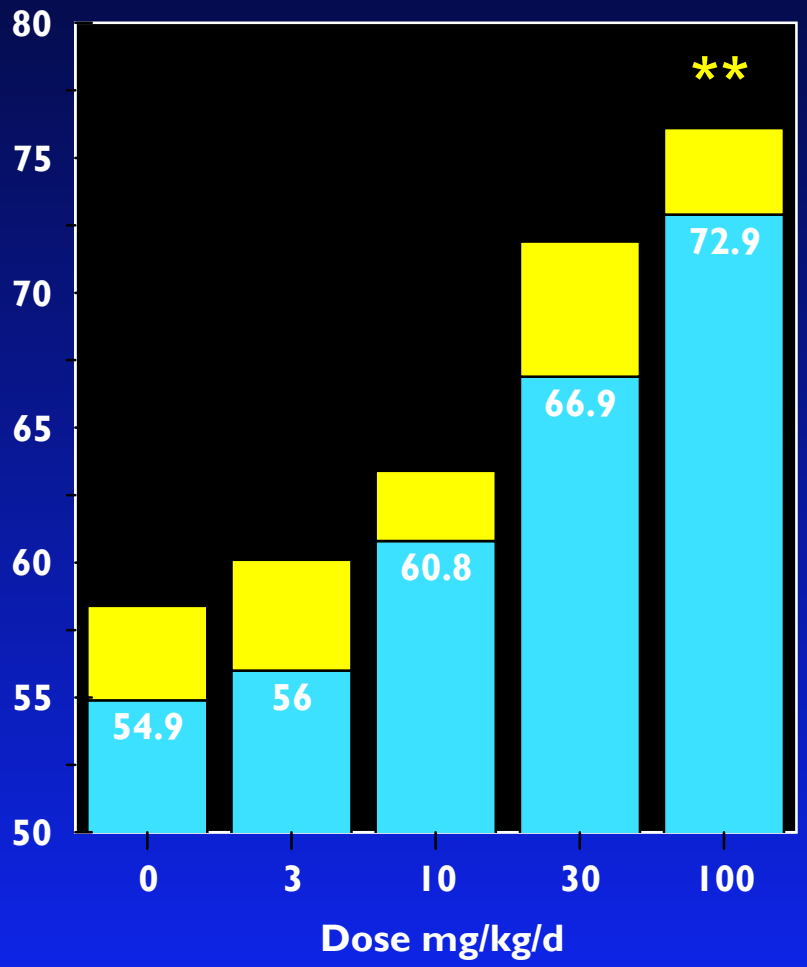


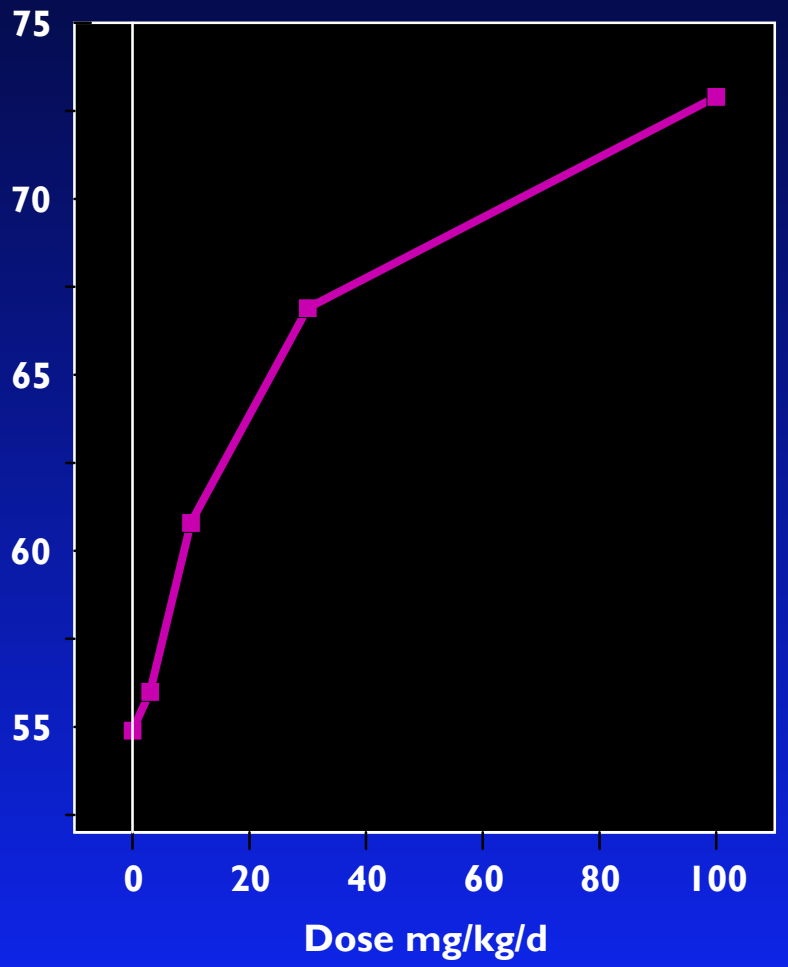
63. Effect of vinclozolin on Cowper's gland weights. Data from four labs



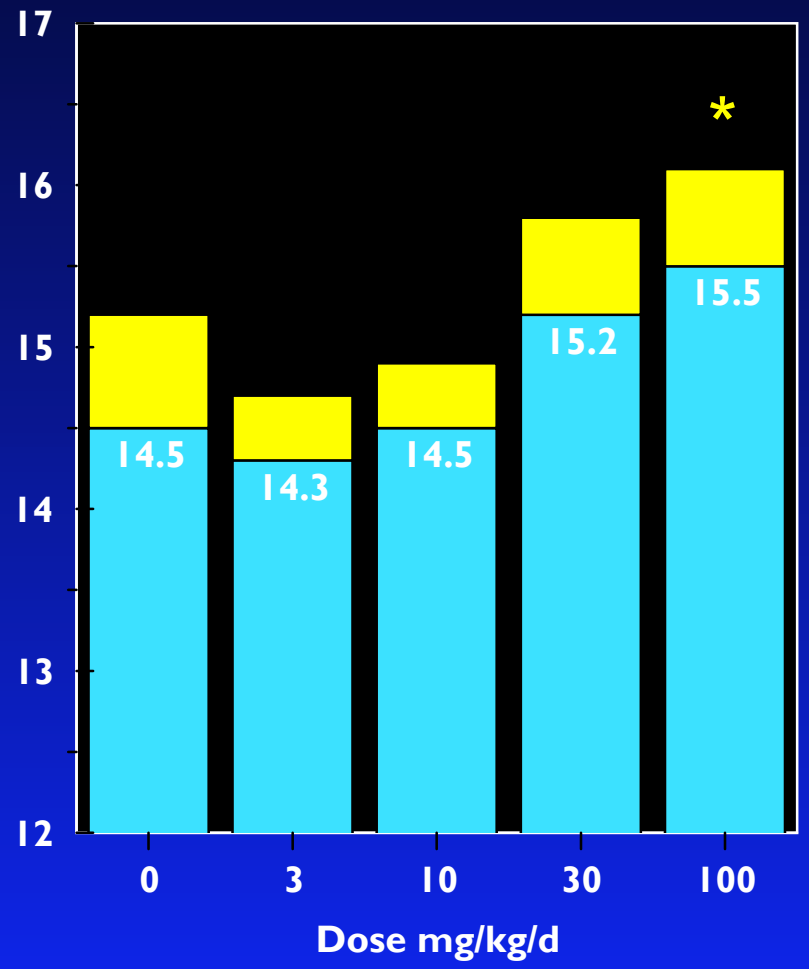


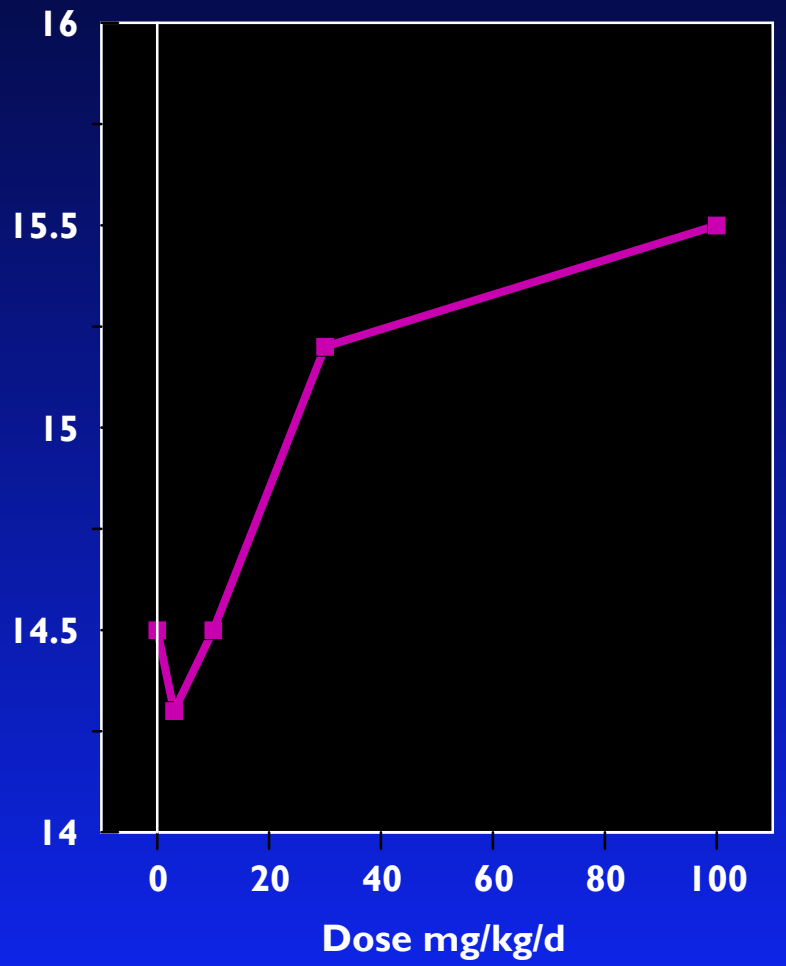
64. Effect of vinclozolin on adrenal weights. Data from one lab



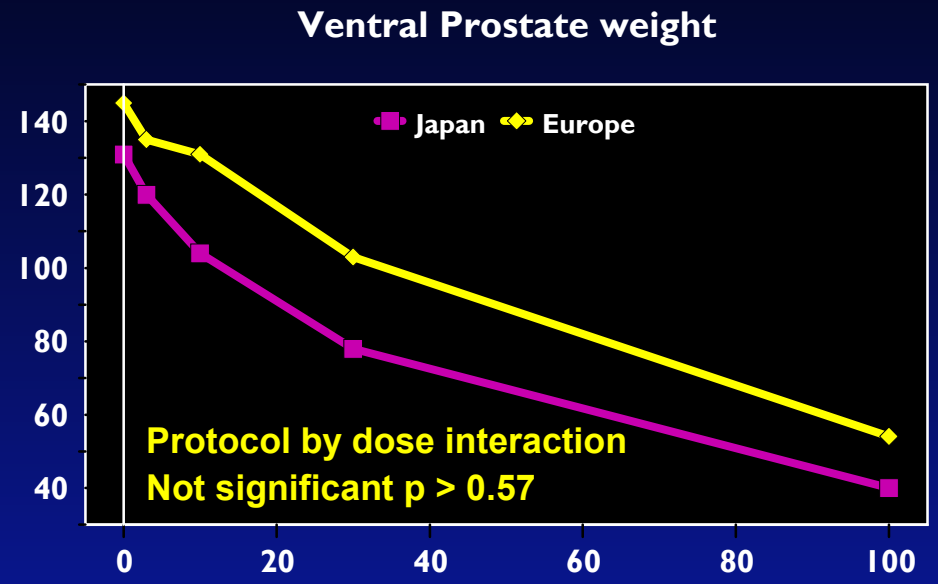


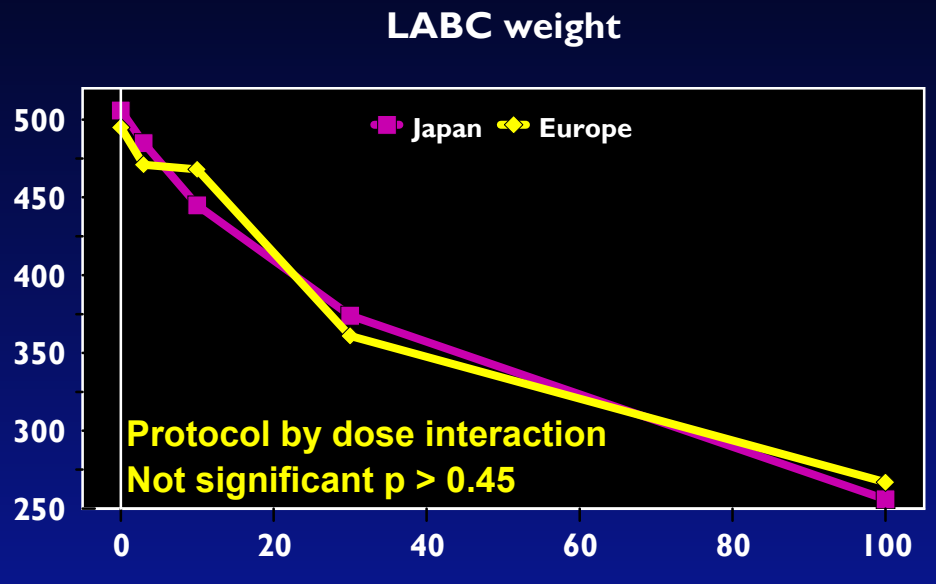
65. Effect of vinclozolin on liver weights. Data from one lab

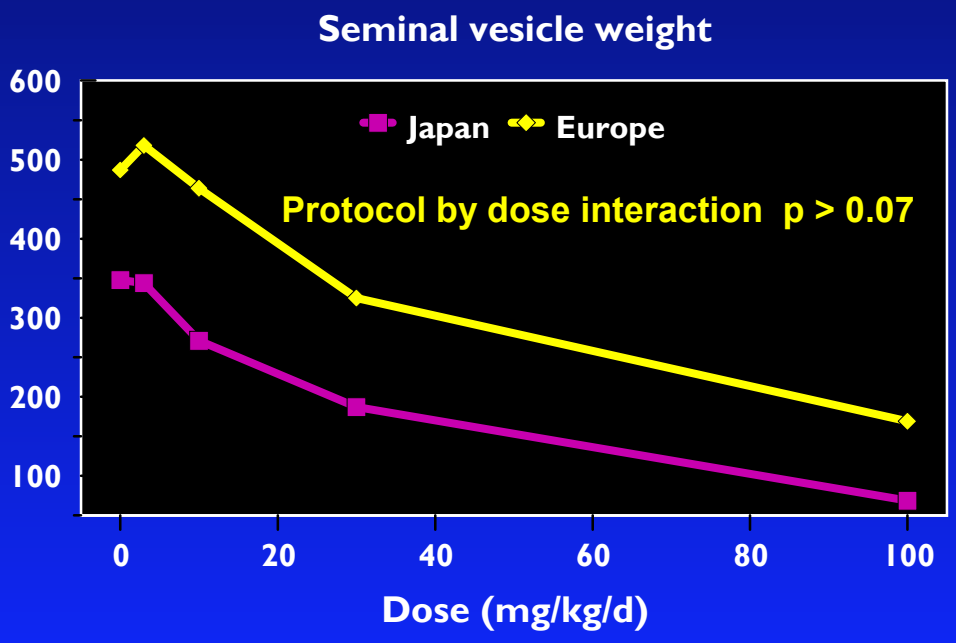


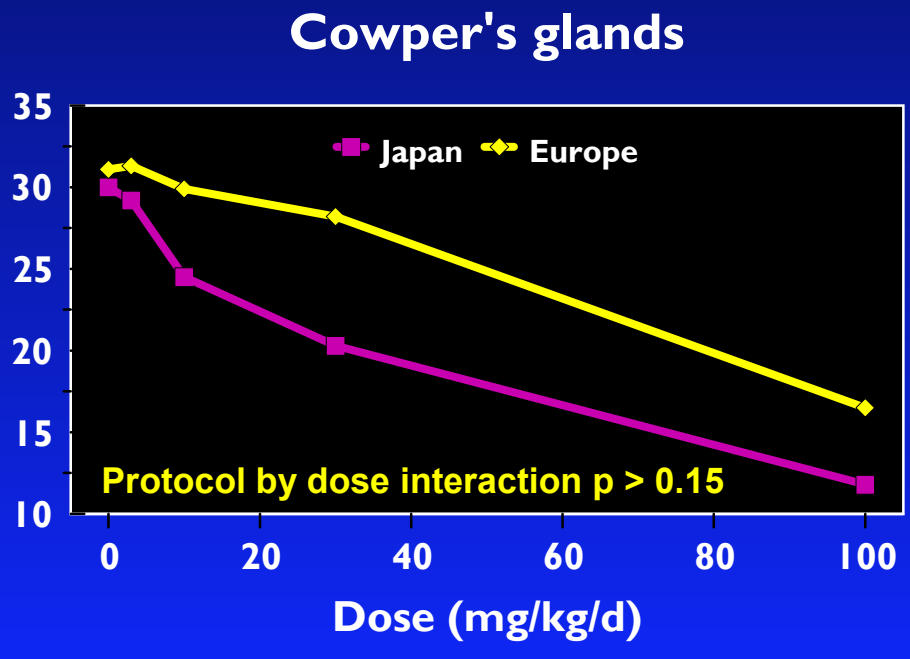


66. Effect of vinclozolin on androgen-dependent organs from the Japanese (using 0.2 mg TP/kg/d) and "European" (using 0.4 mg TP/kg/d) studies.

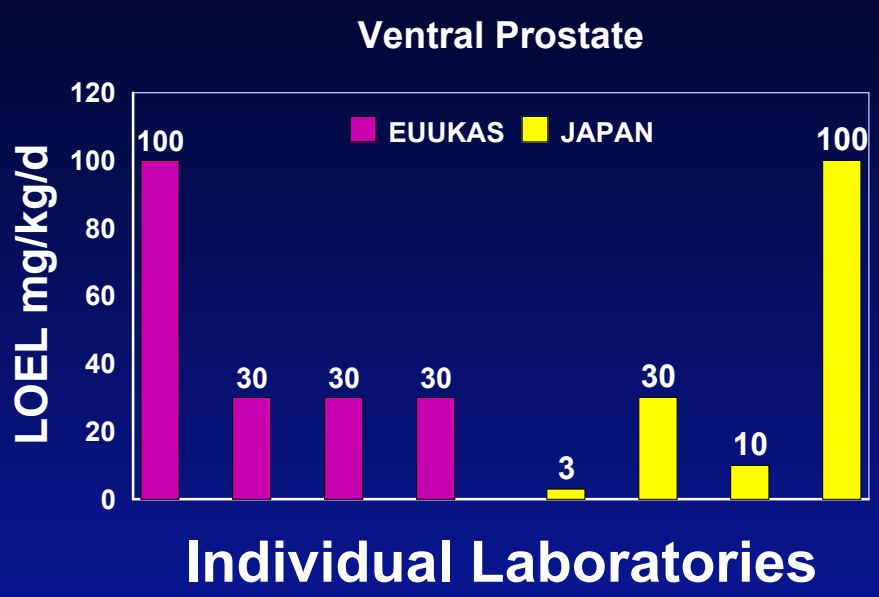


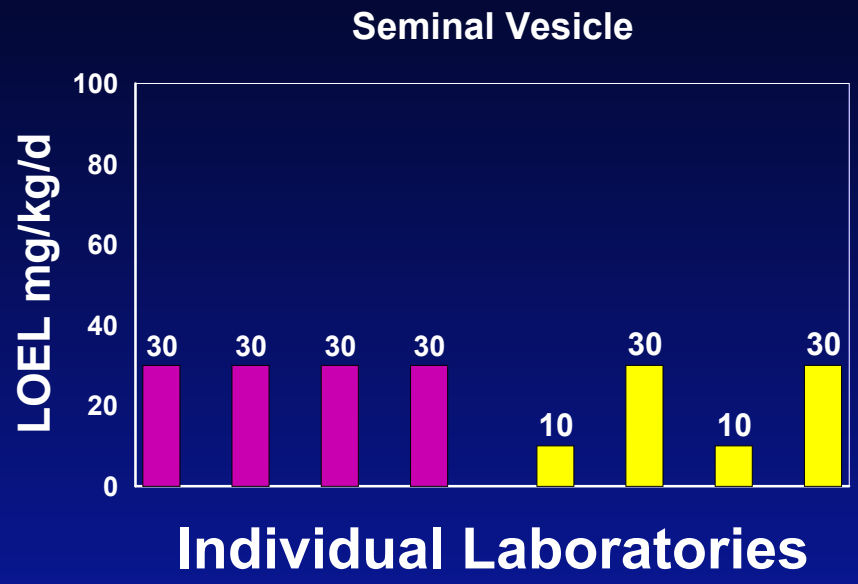


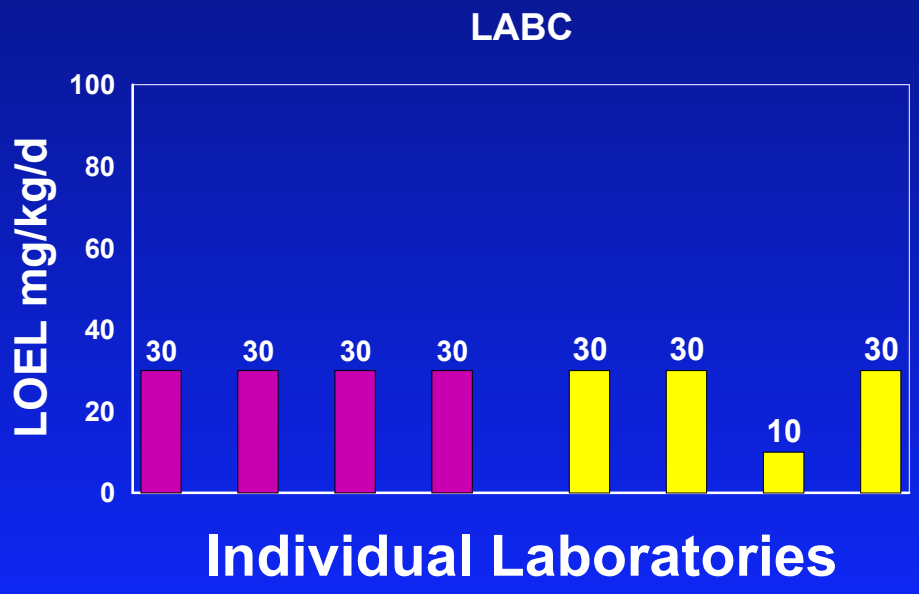


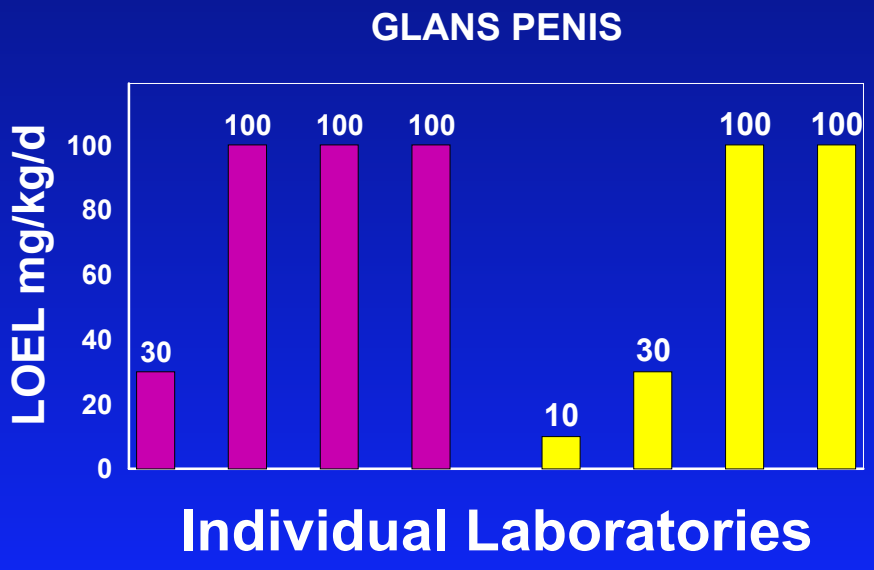


67. Comparison of Vinclozolin data from Japan and "Europe" based upon observed LOELs









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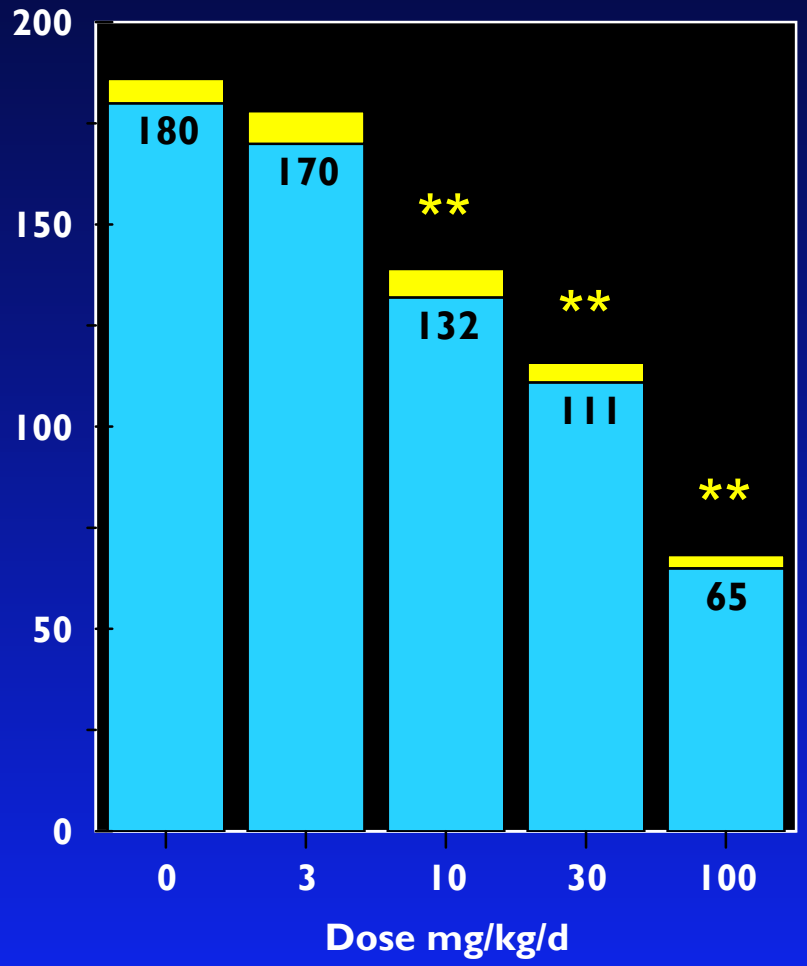
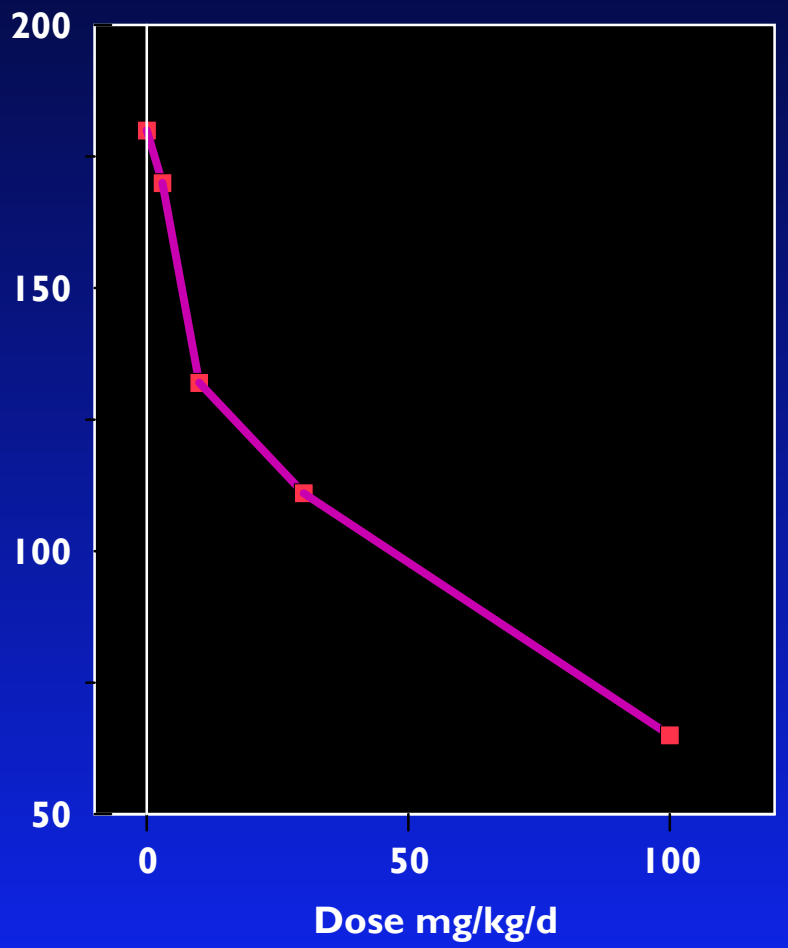
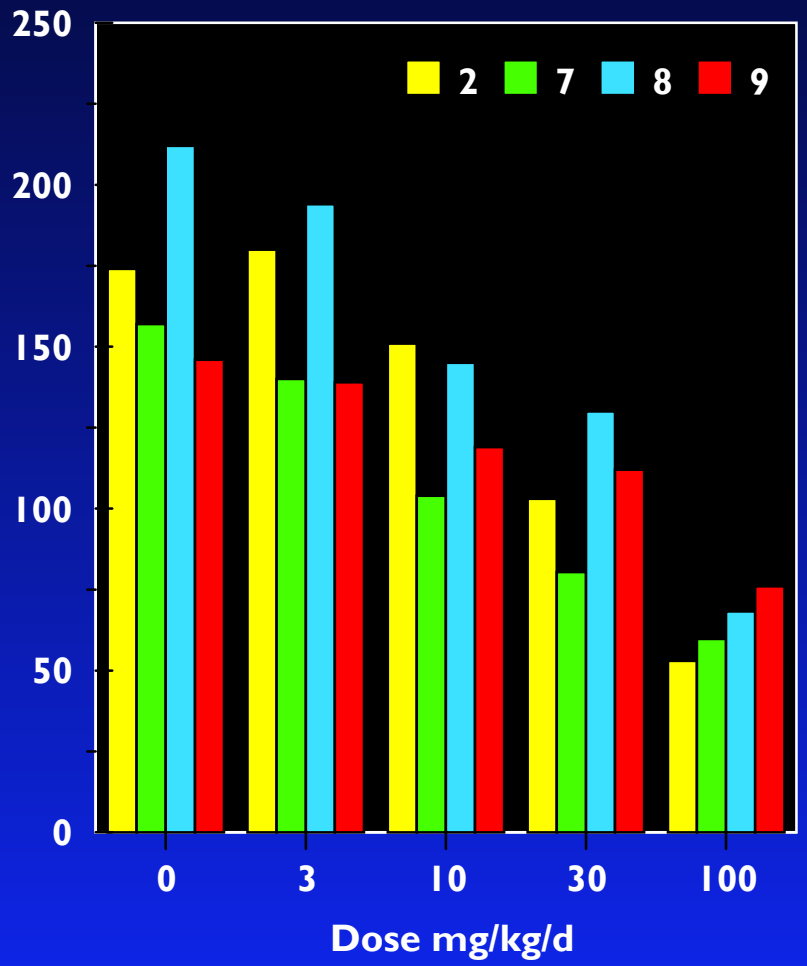
Procymidone data

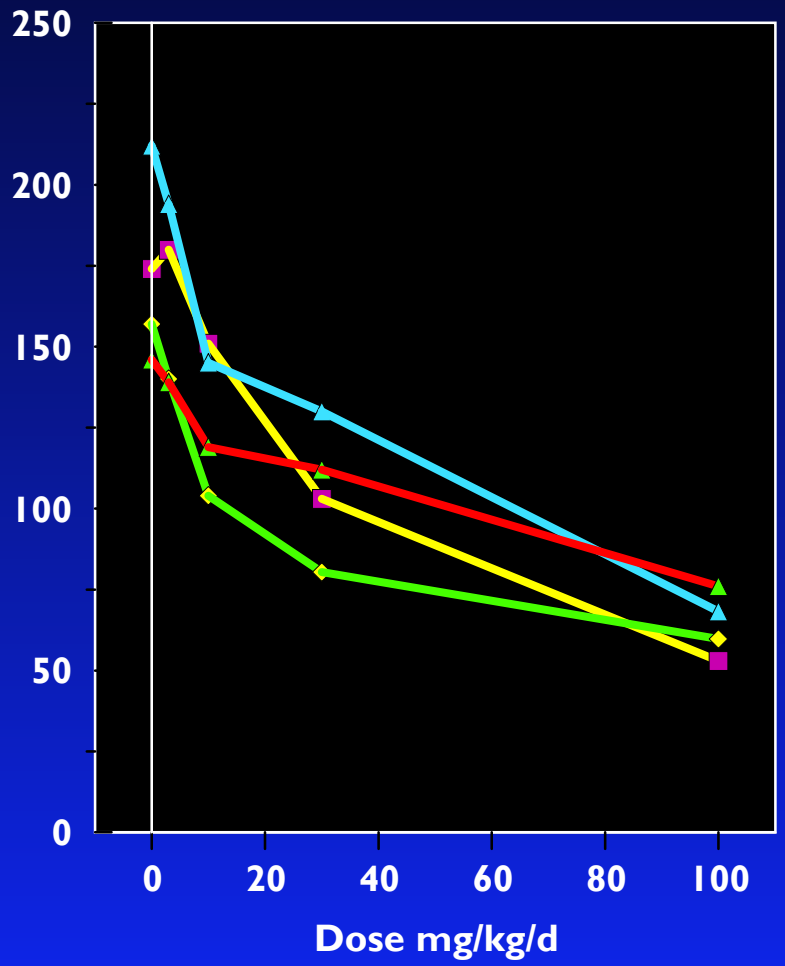
68. Effect of Procymidone on Ventral Prostate weights. Data from four labs



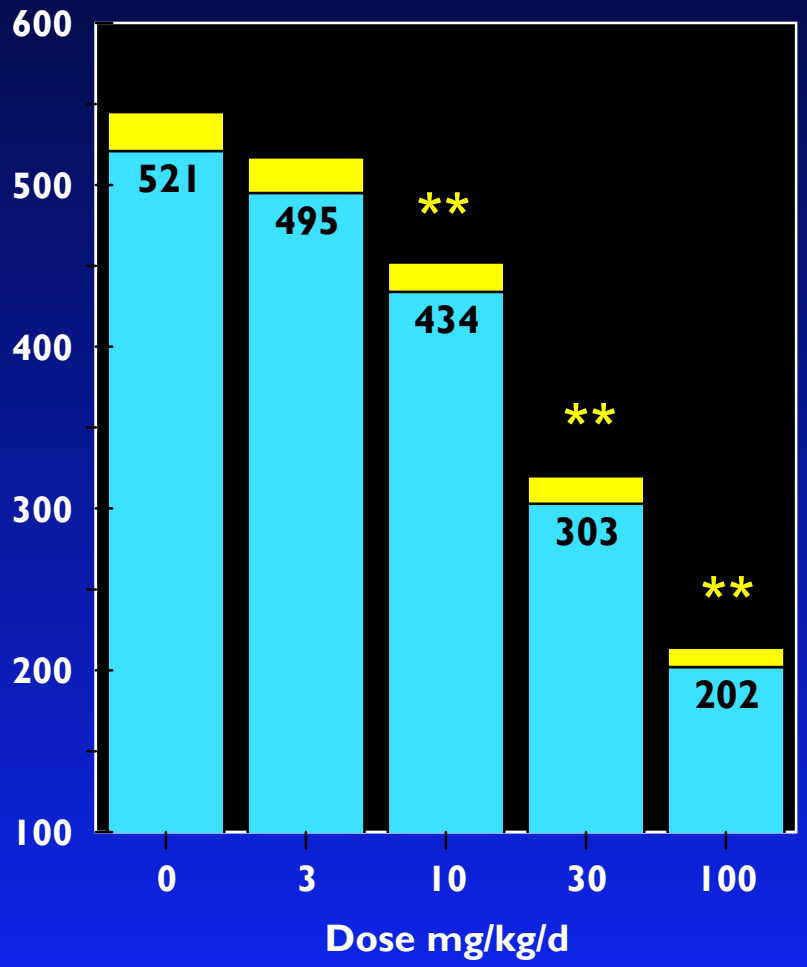


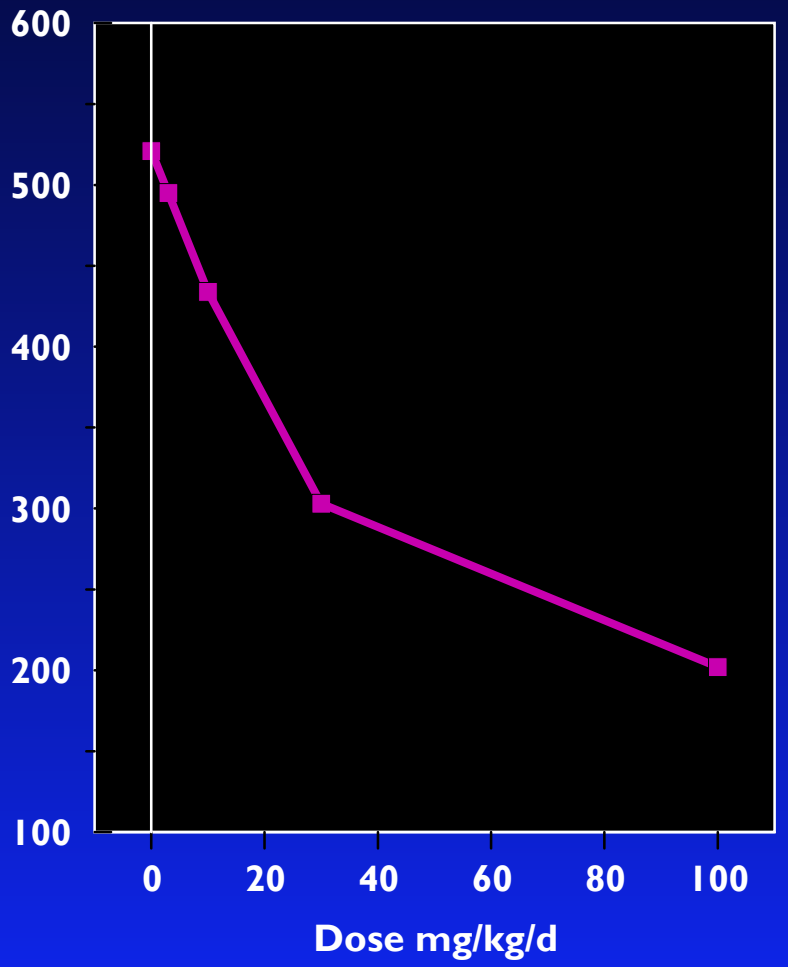
69. Effect of Procymidone on VP weights. Data from four labs



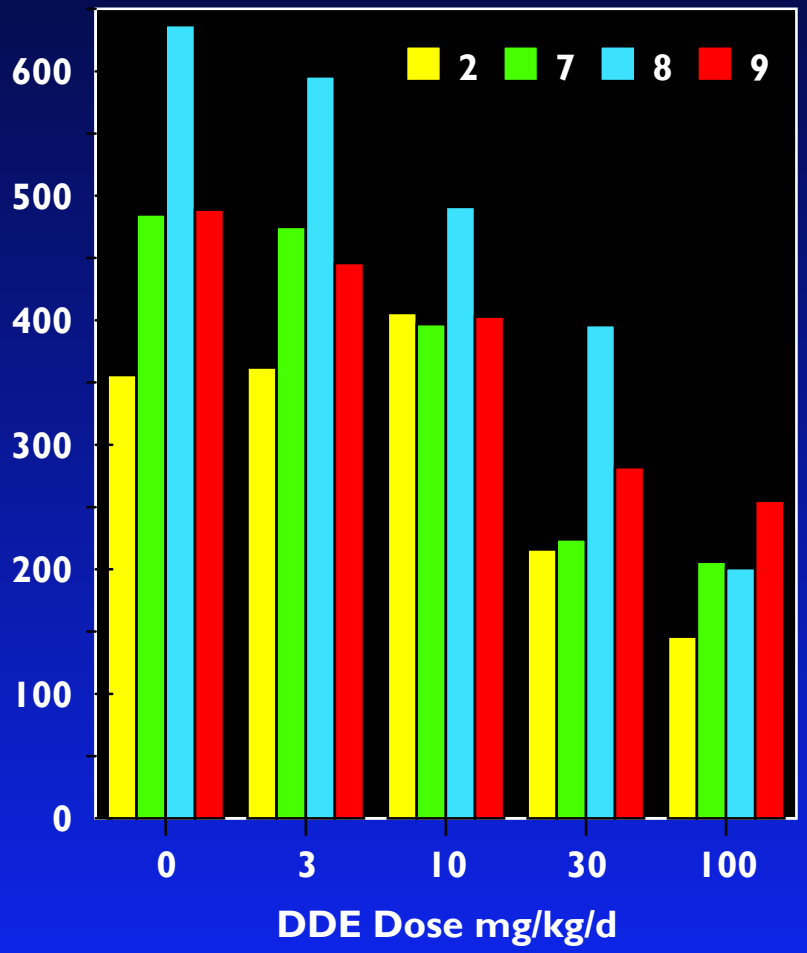


70. Effect of Procymidone on Seminal Vesicle weights. Data from four labs

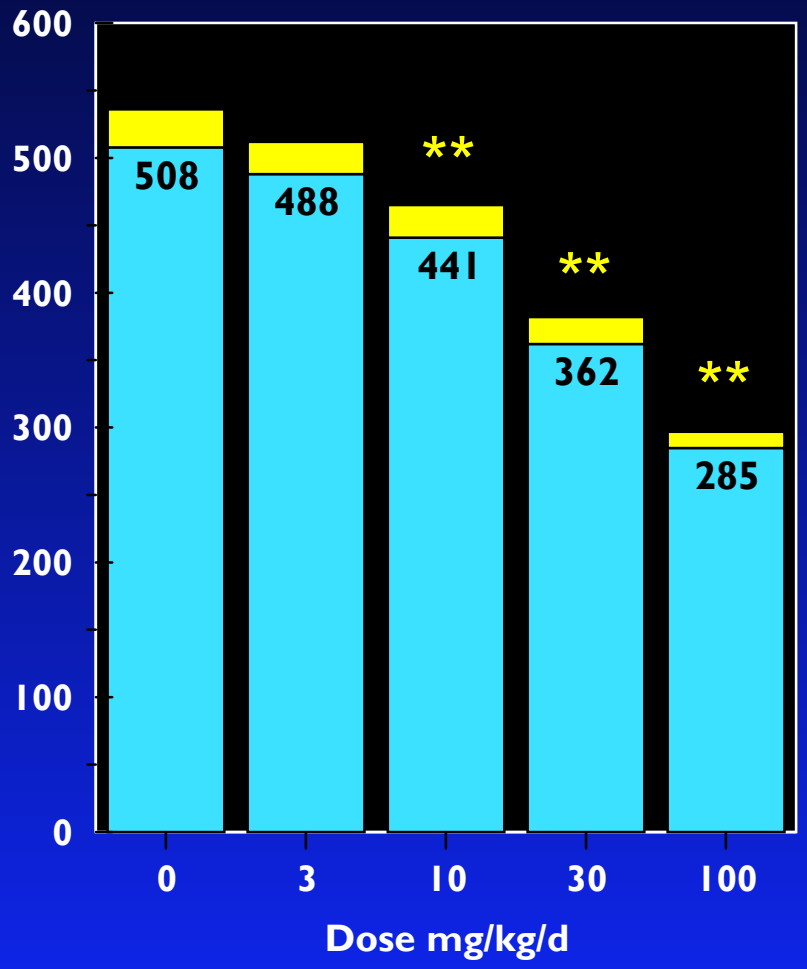




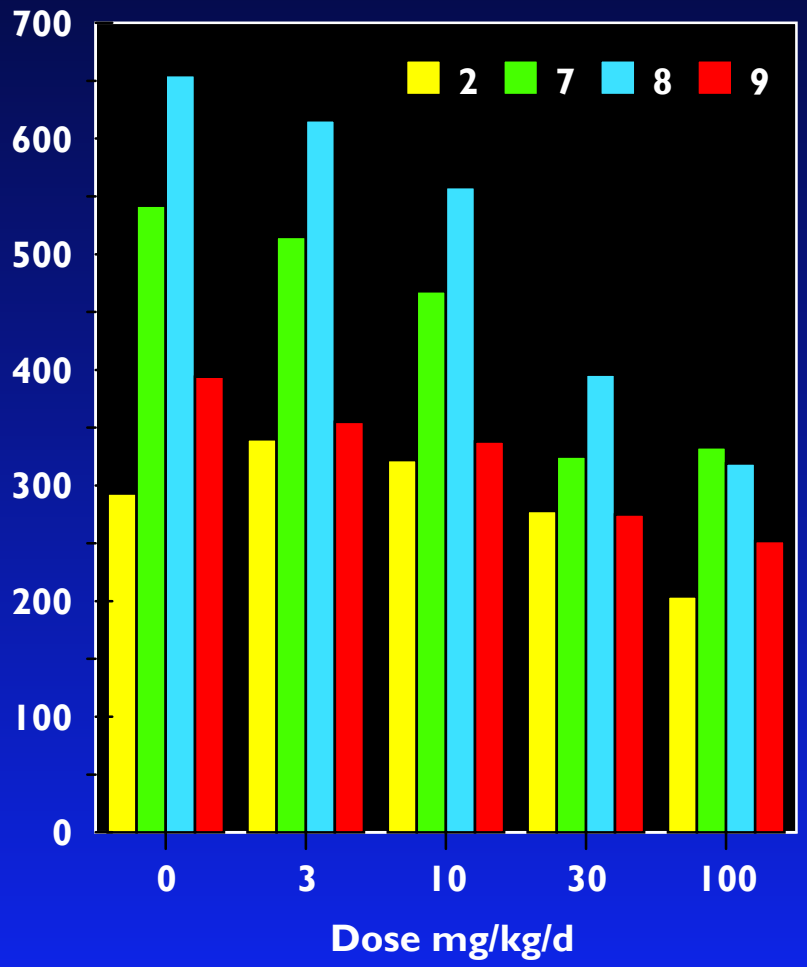
71. Effect of Procymidone on Seminal Vesicle weights. Data from four labs

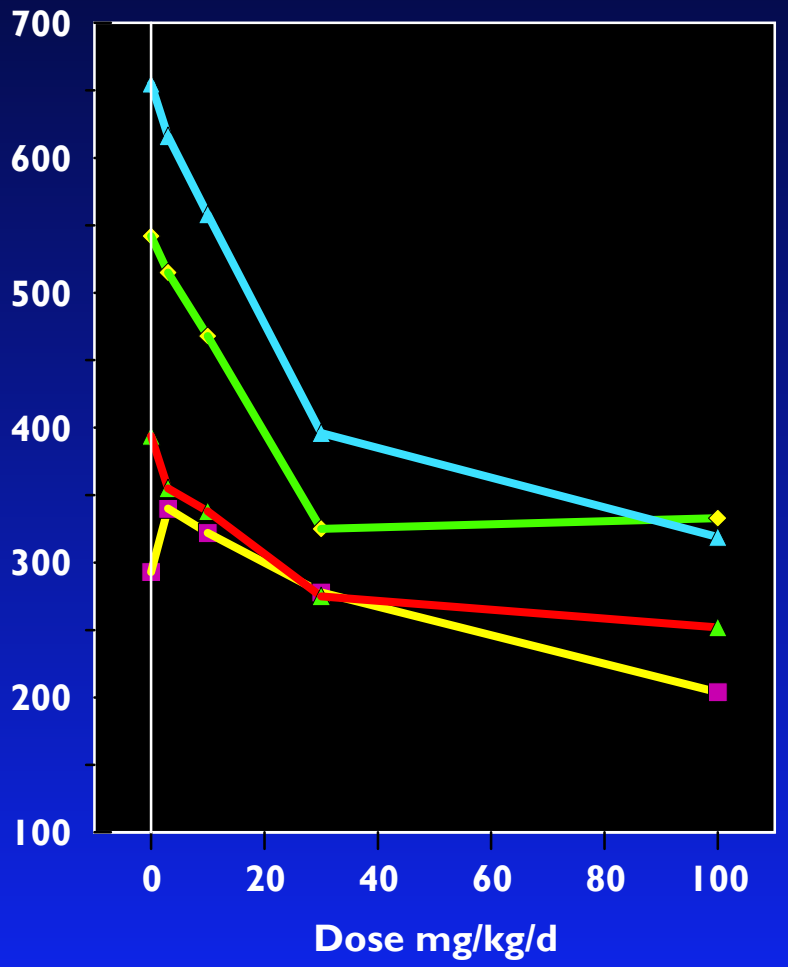


72. Effect of Procymidone on LABC weights. Data from four labs

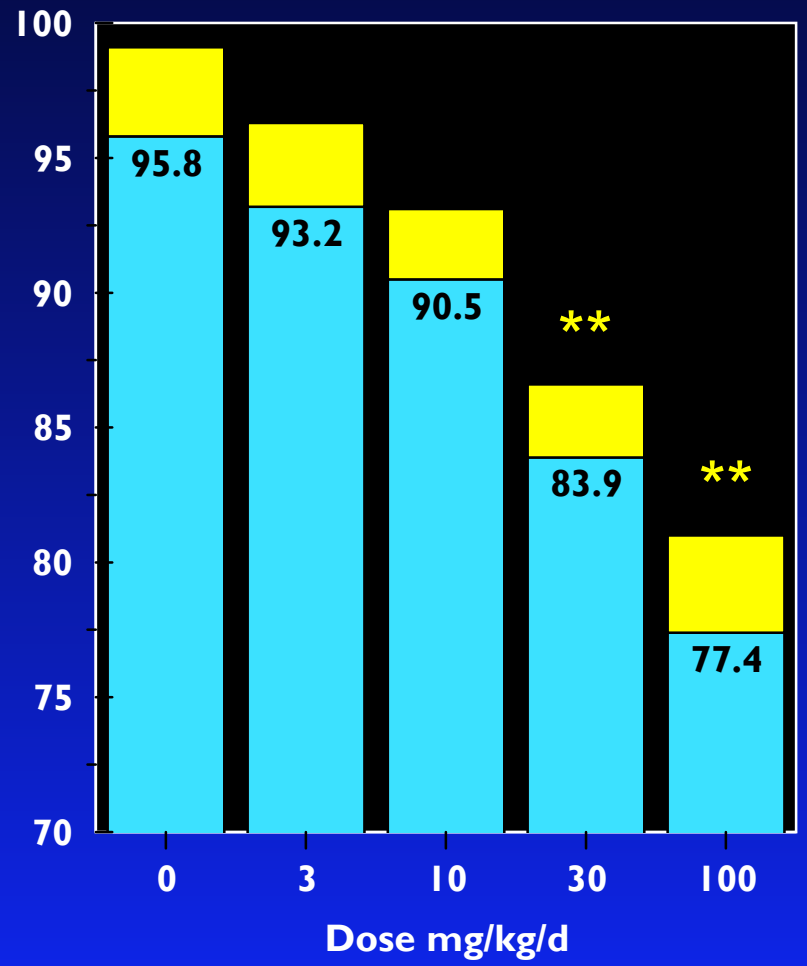


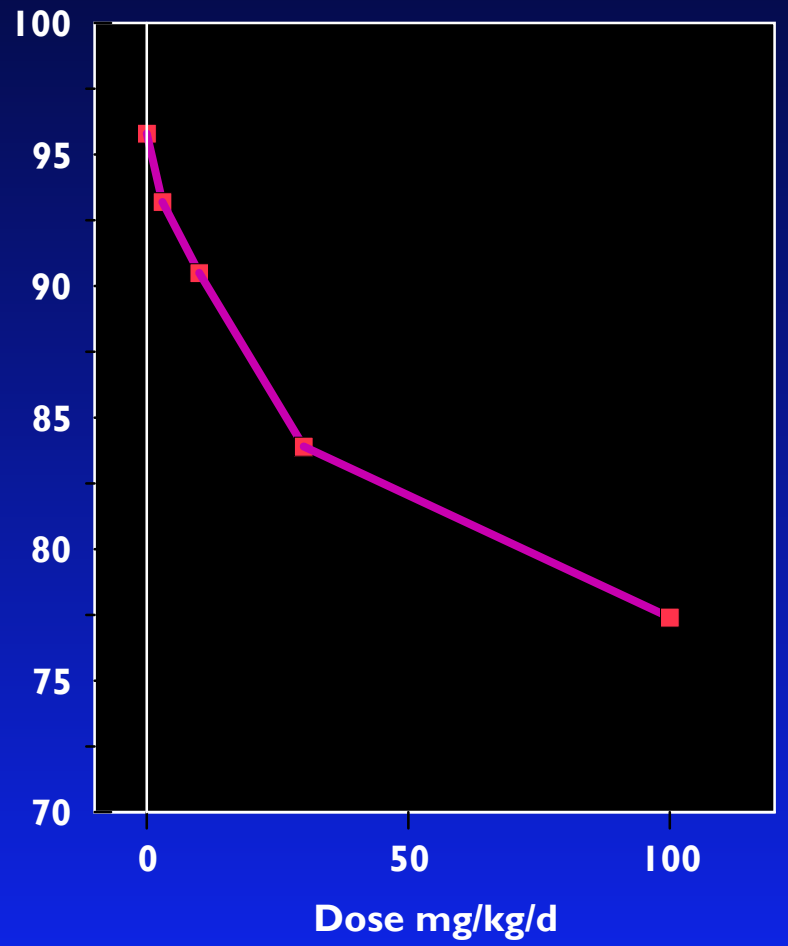
73. Effect of Procymidone on LABC weights. Data from four labs



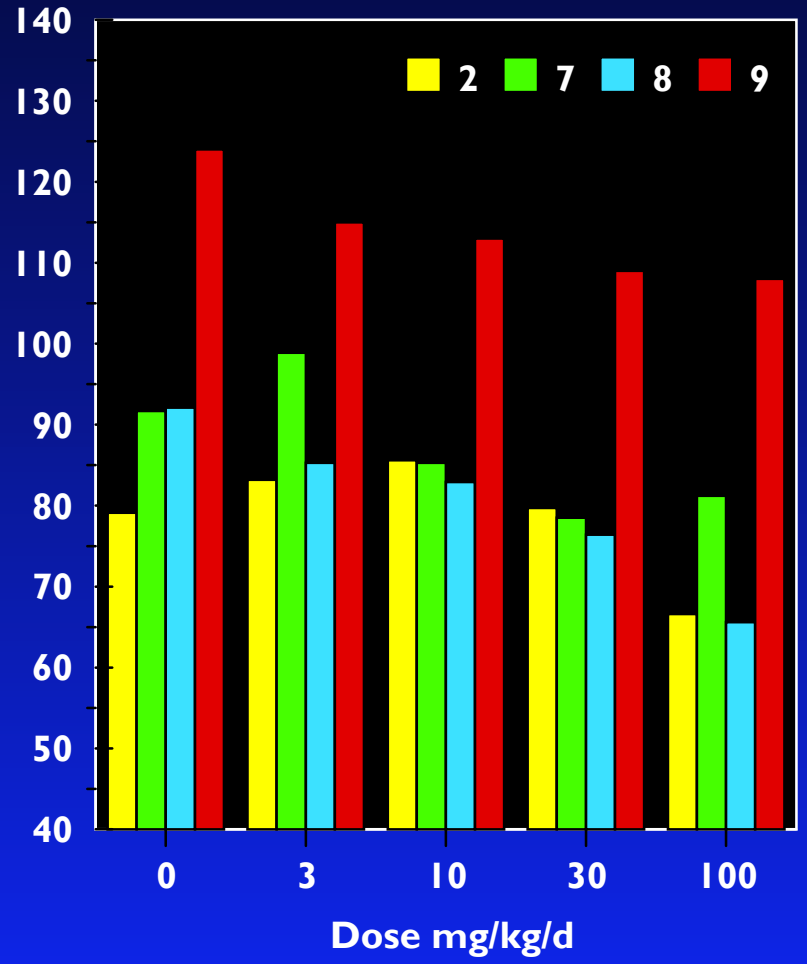


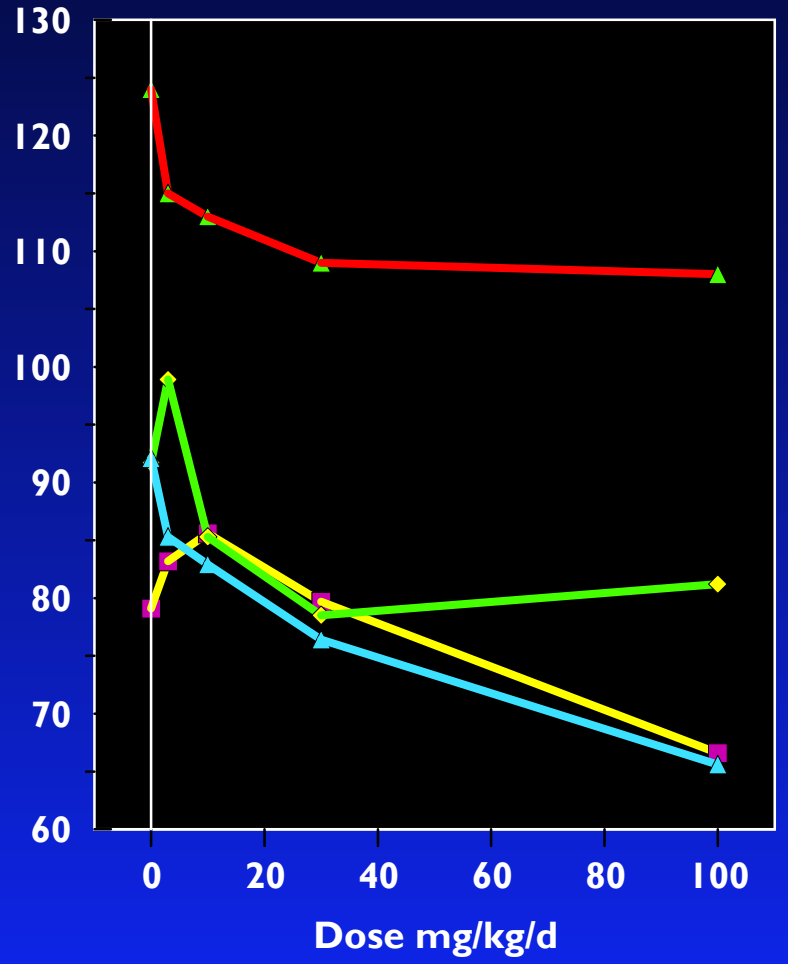
74. Effect of Procymidone on Glans penis weights. Data from four labs



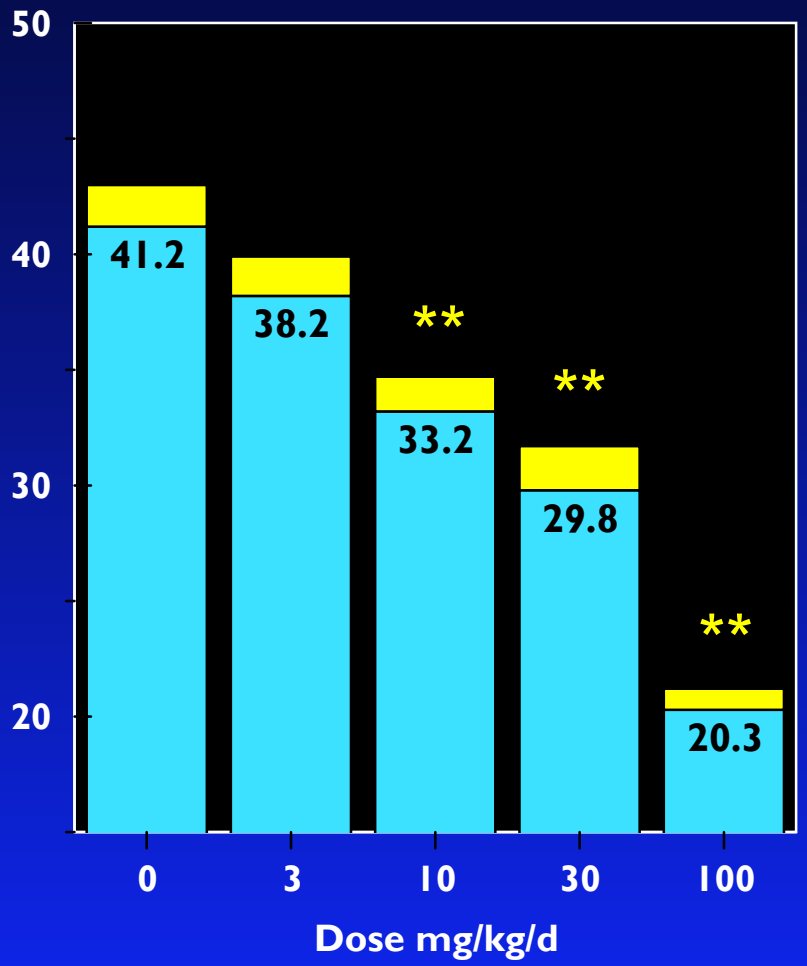


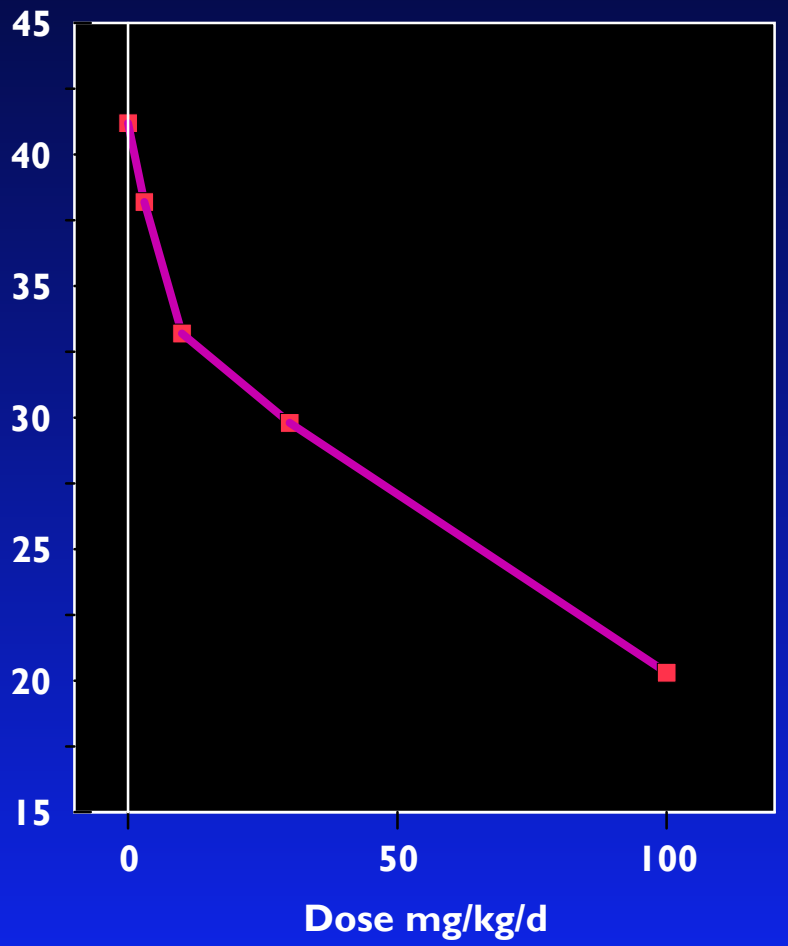
75. Effect of Procymidone on Glans Penis weights. Data from four labs



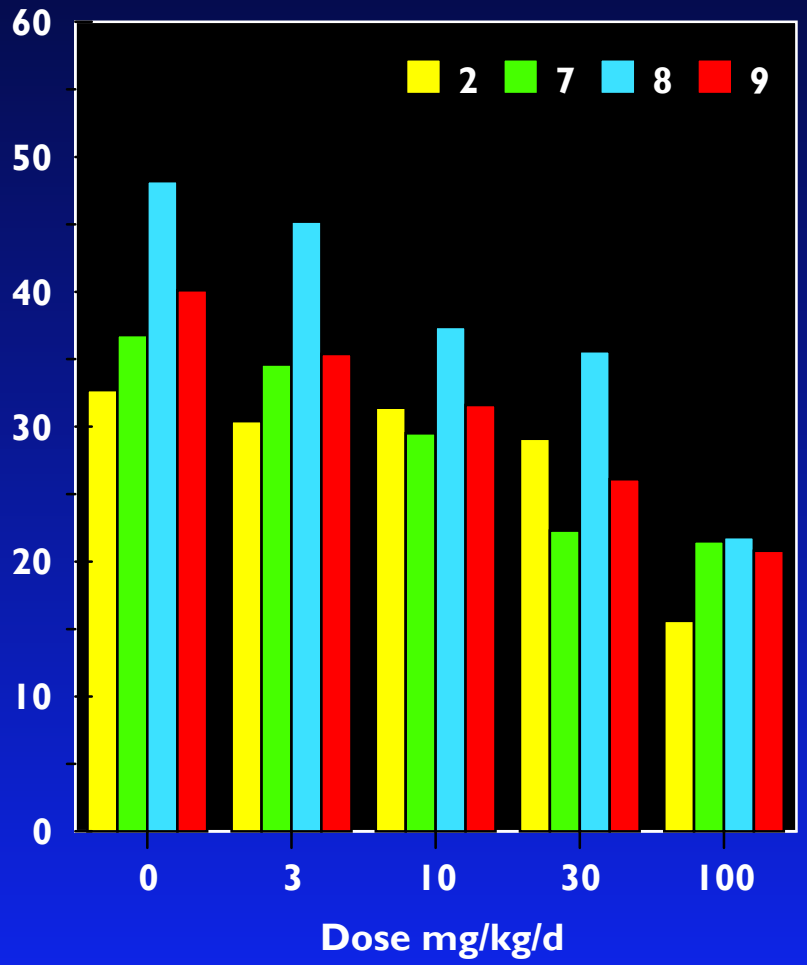


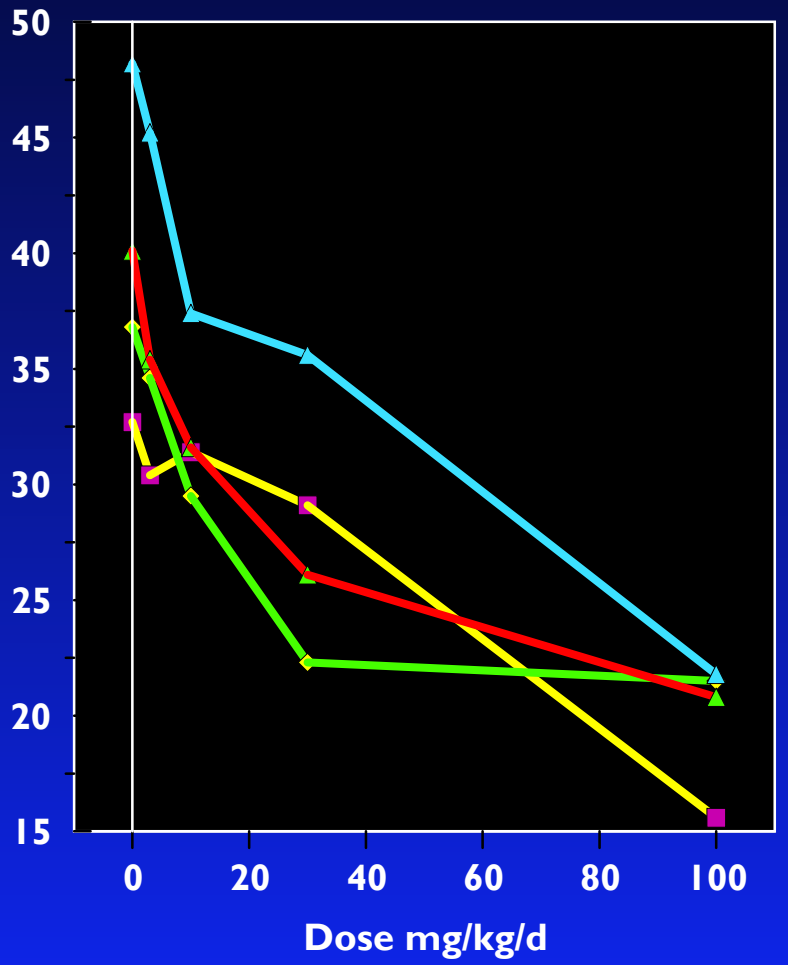
76. Effect of Procymidone on Cowper's gland weights. Data from four labs



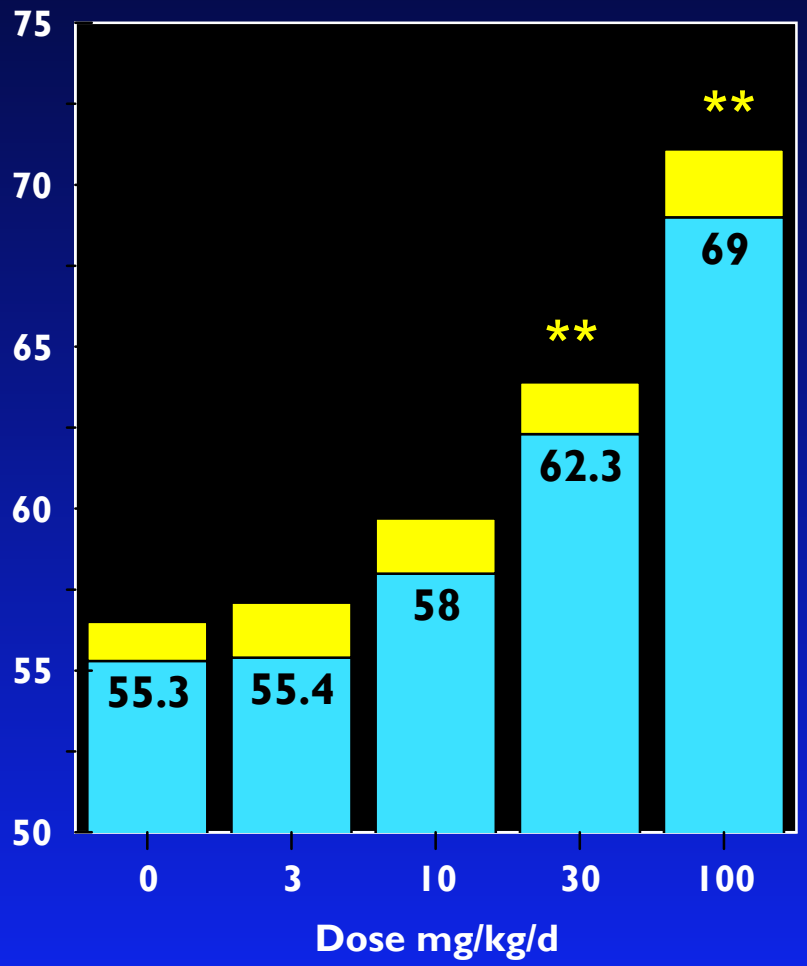


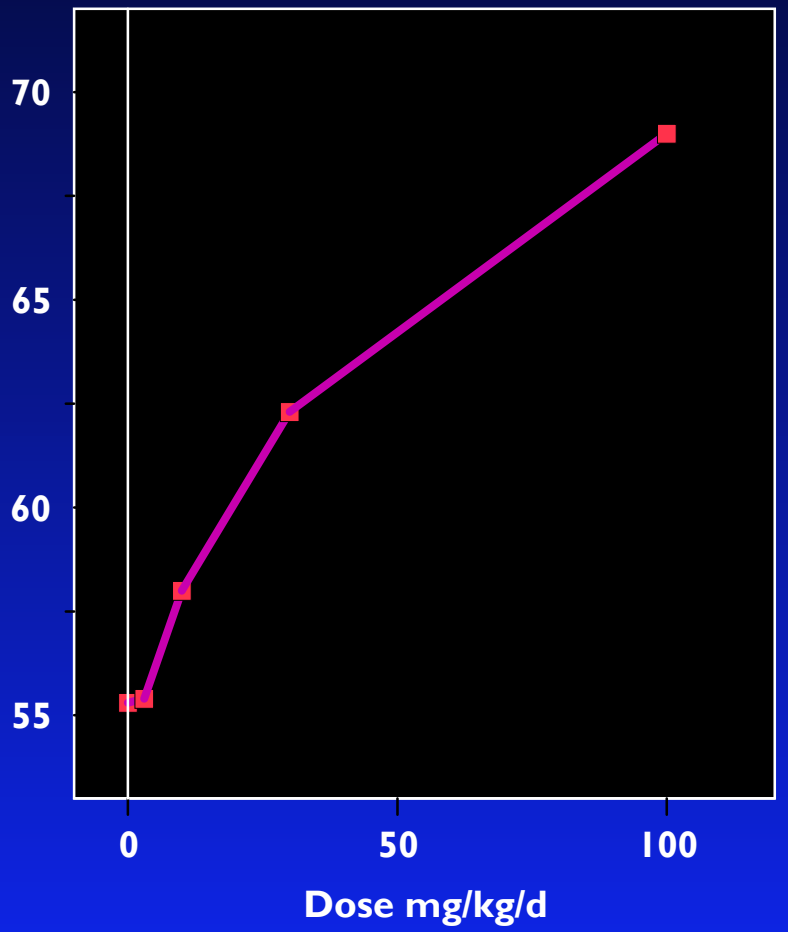
77. Effect of Procymidone on Cowper's gland weights. Data from four labs



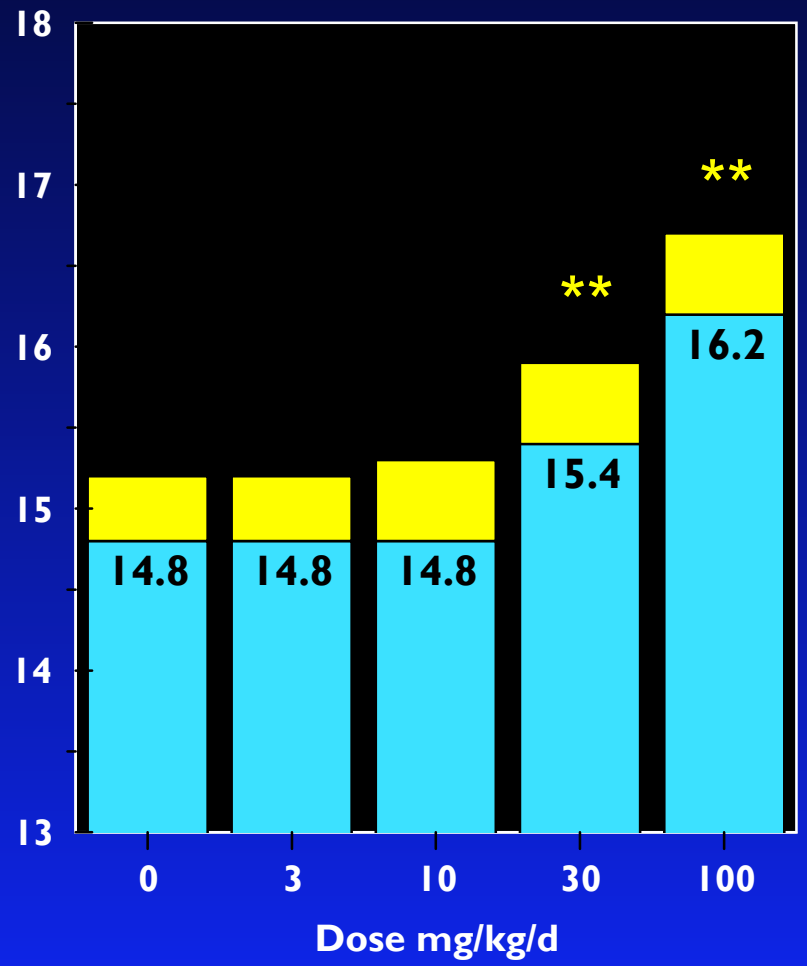


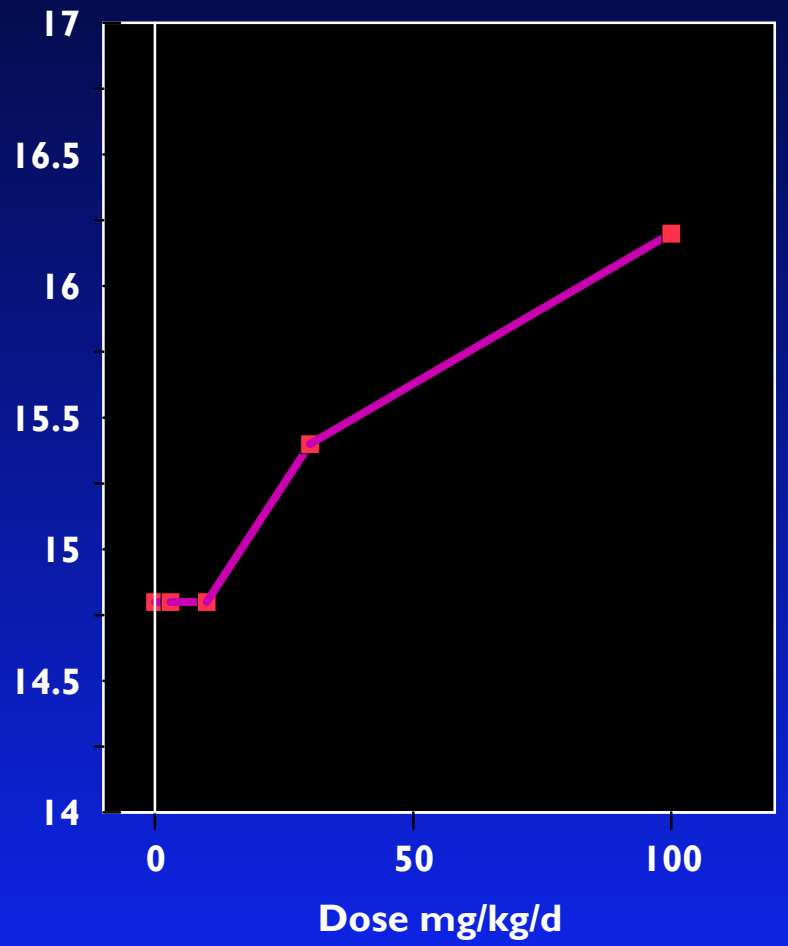
78. Effect of Procymidone on Adrenal weights. Data from four labs



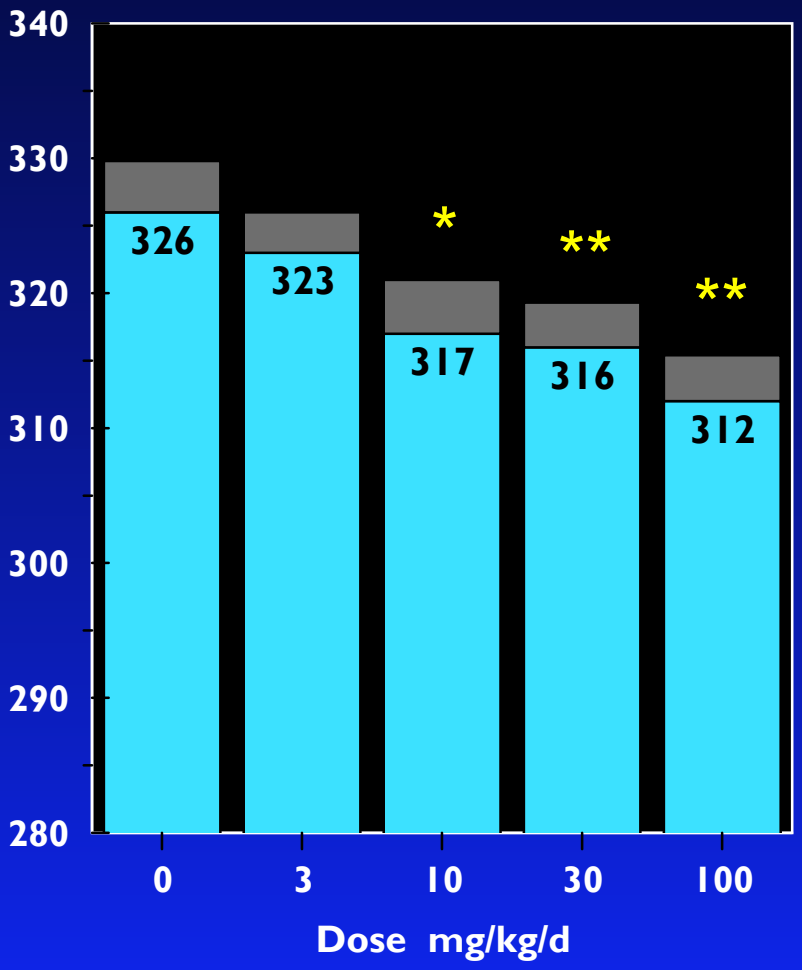


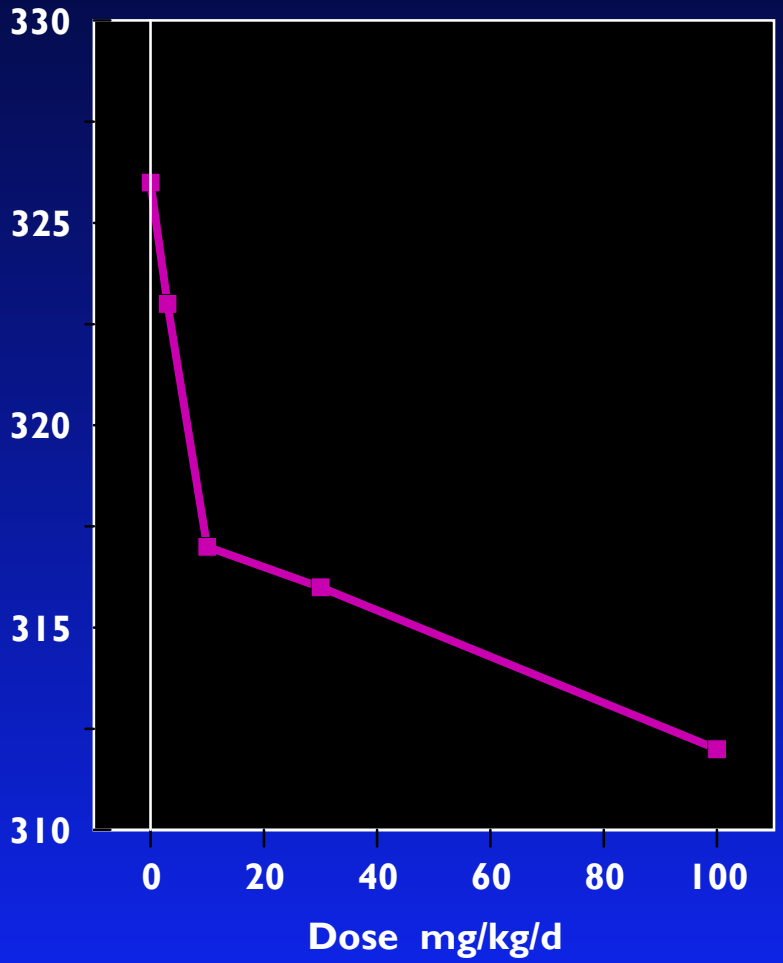
79. Effect of Procymidone on Liver weights. Data from four labs





80. Effects of Procymidone on Body weight at necropsy - 4 LABS





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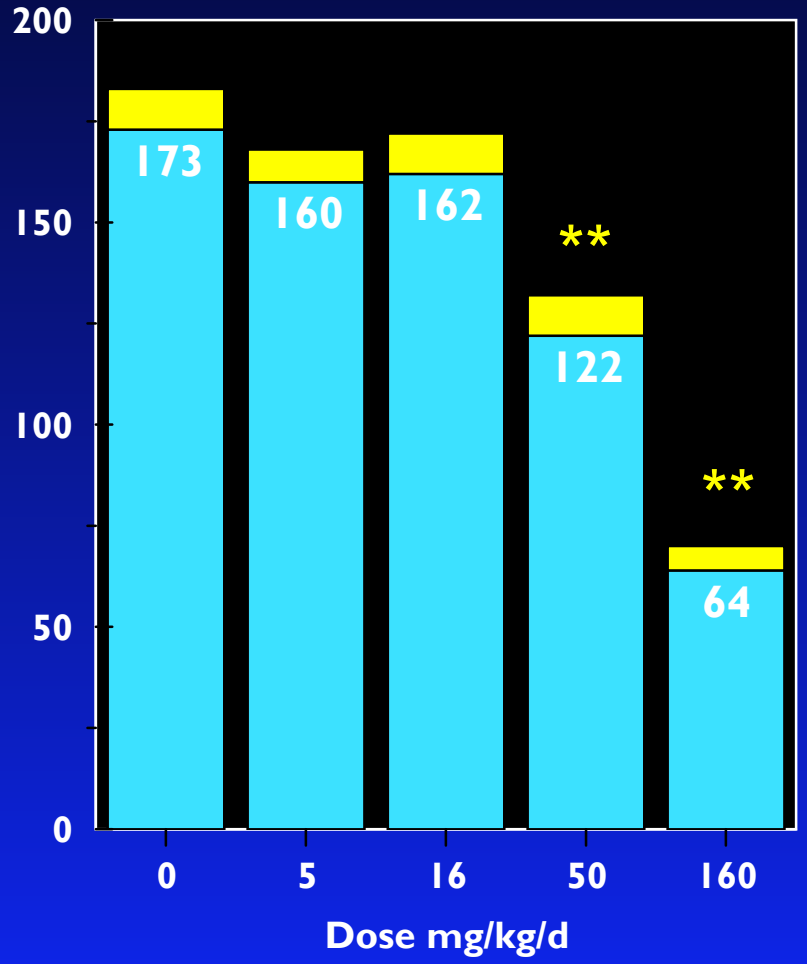
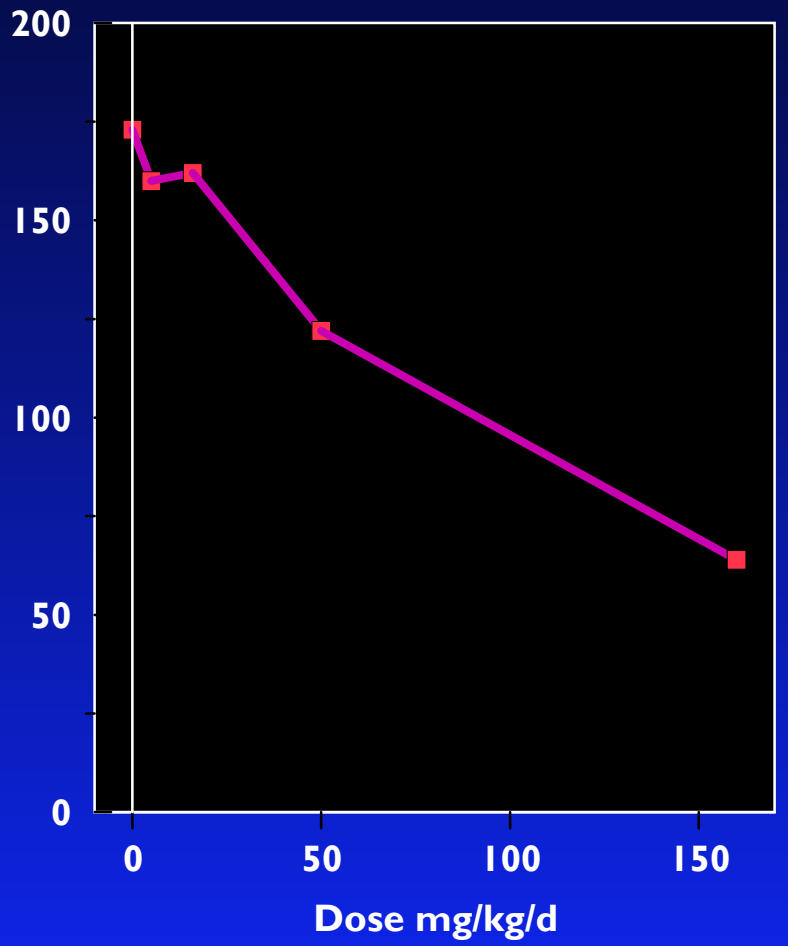
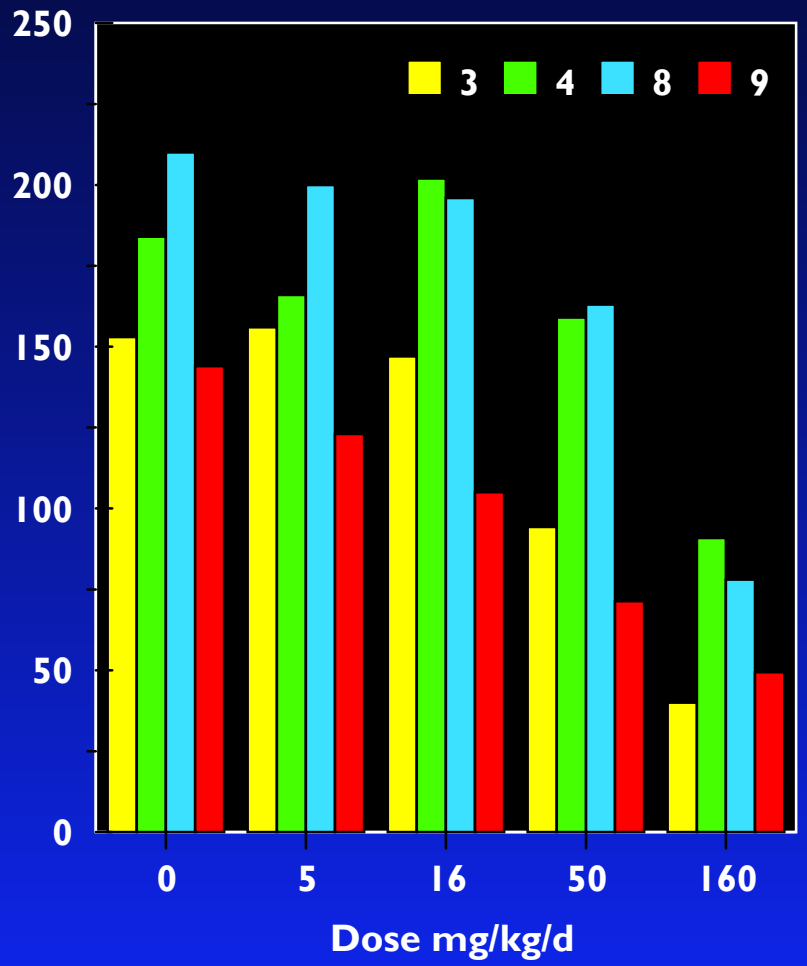
p,p' DDE data

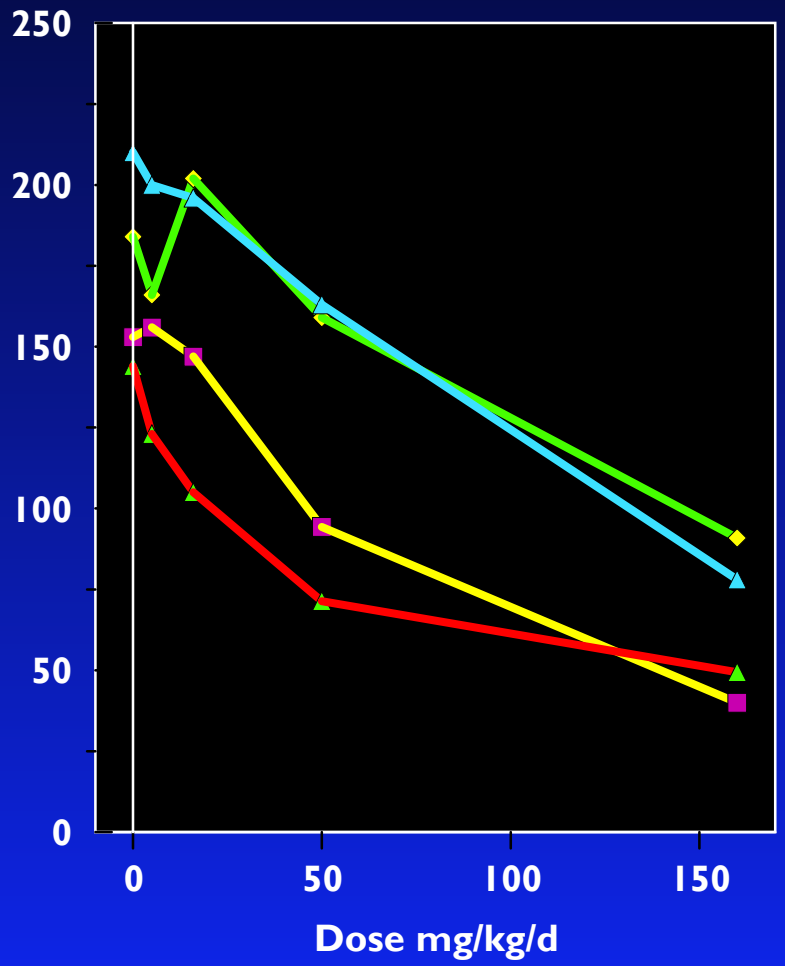
81. Effect of p,p' DDE on Ventral Prostate weights. Data from four labs



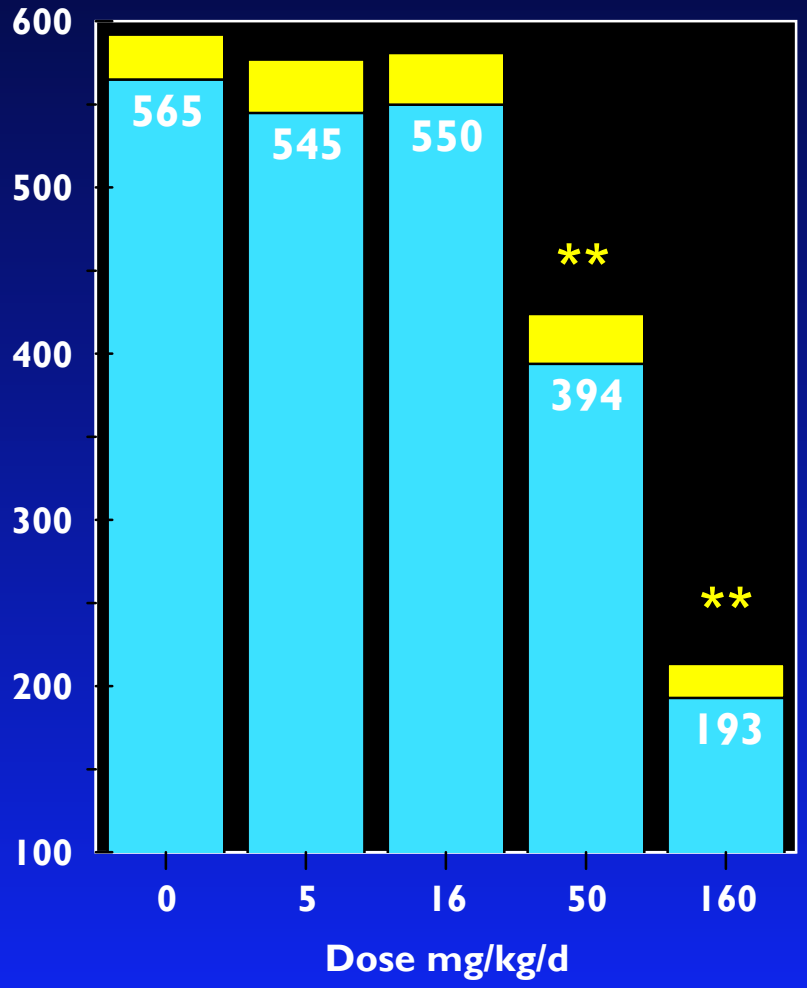


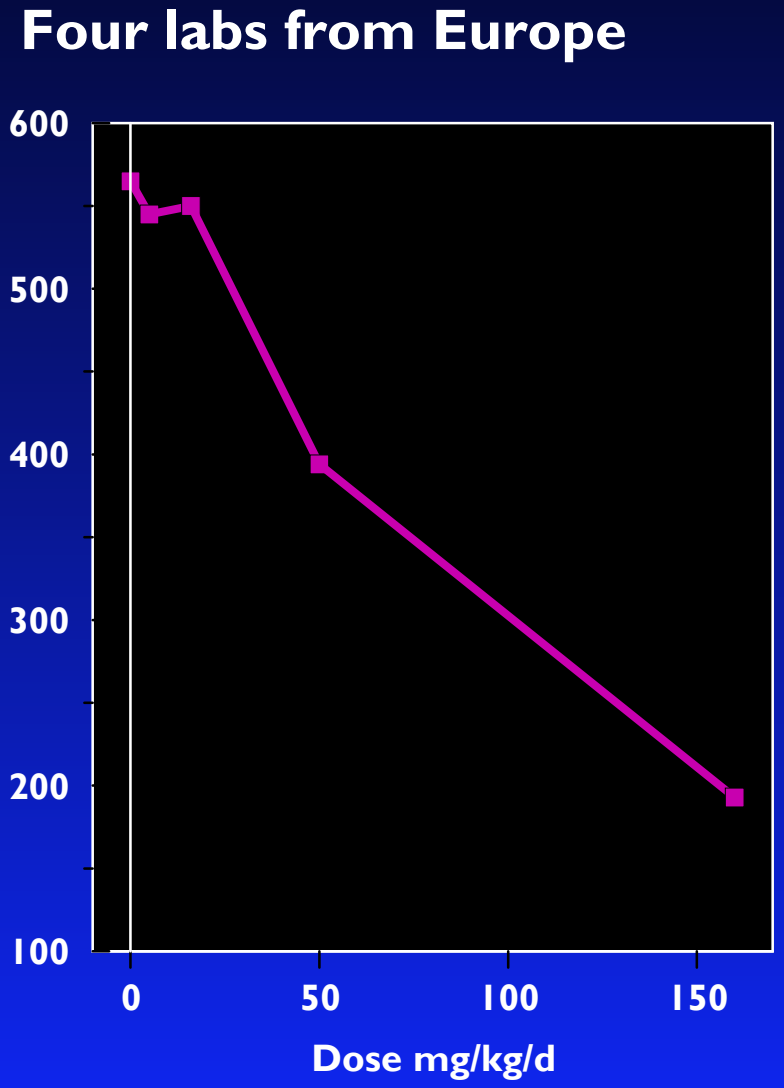
82. Effect of p,p' DDE on VP weights. Data from four labs



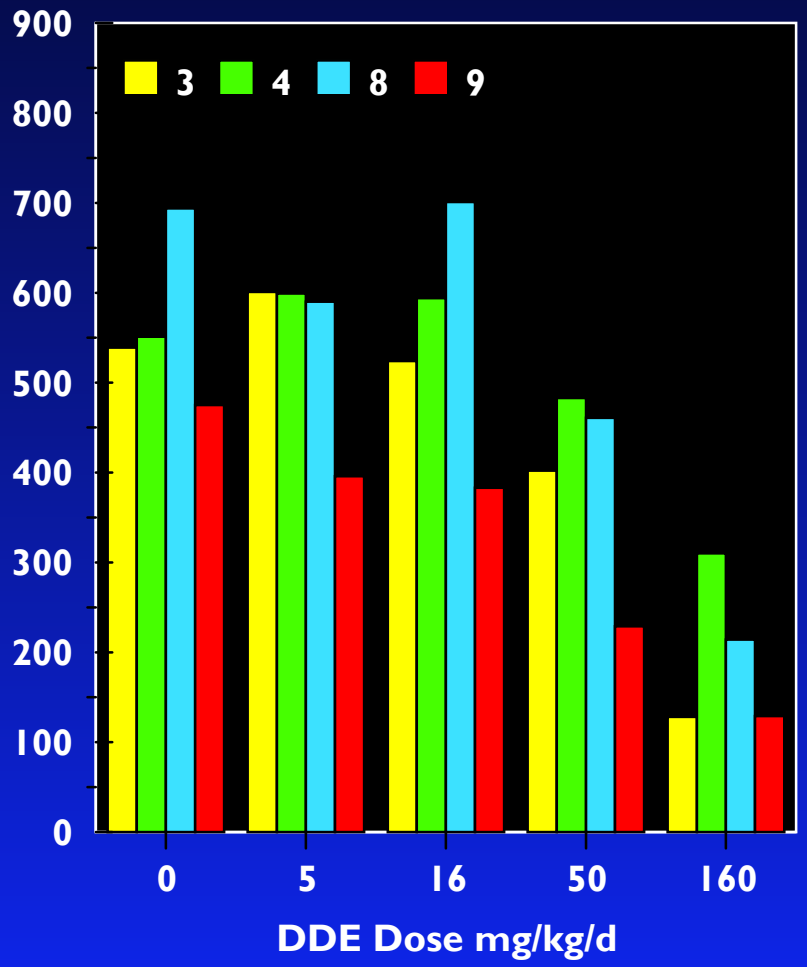


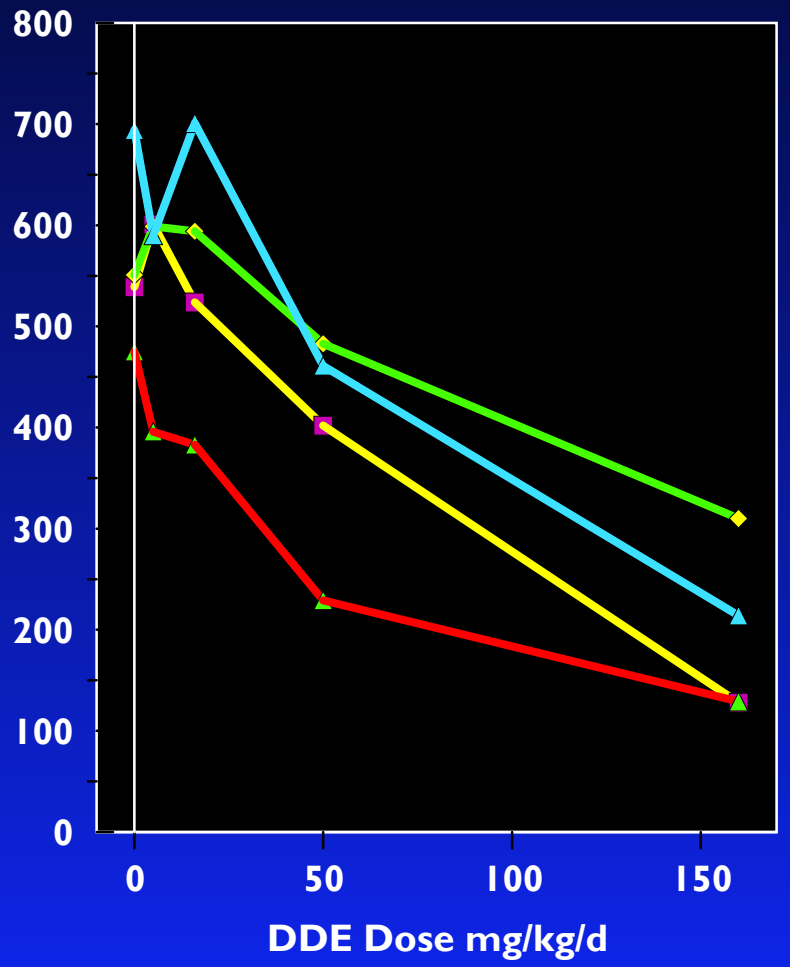
83. Effect of p,p' DDE on Seminal Vesicle weights. Data from four labs



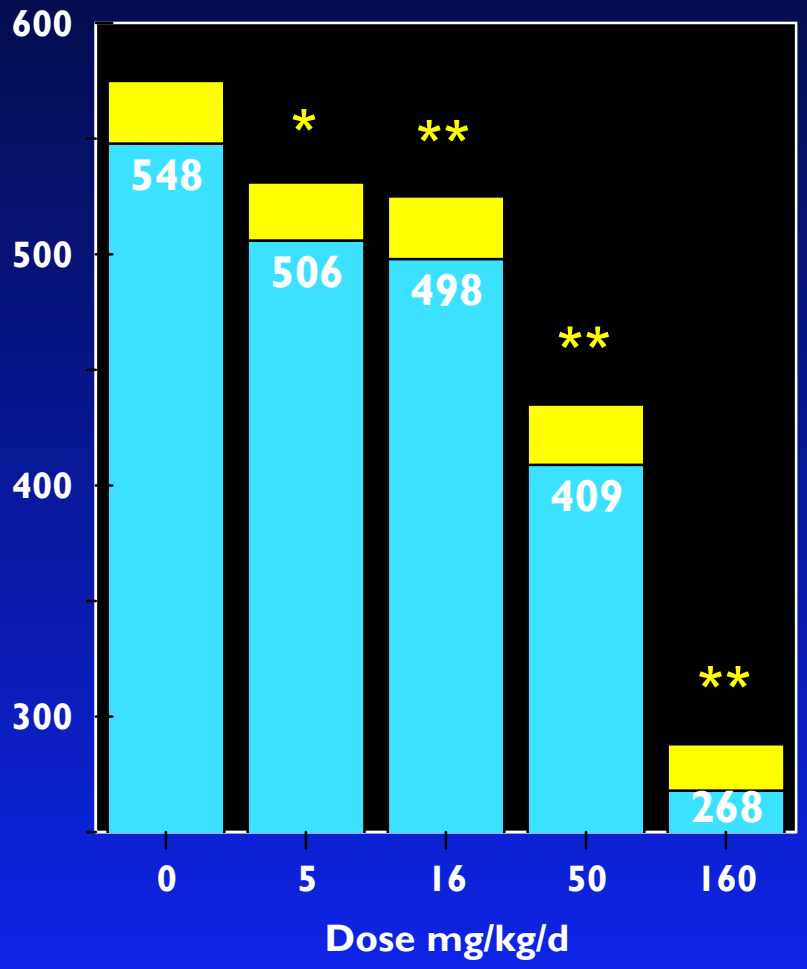


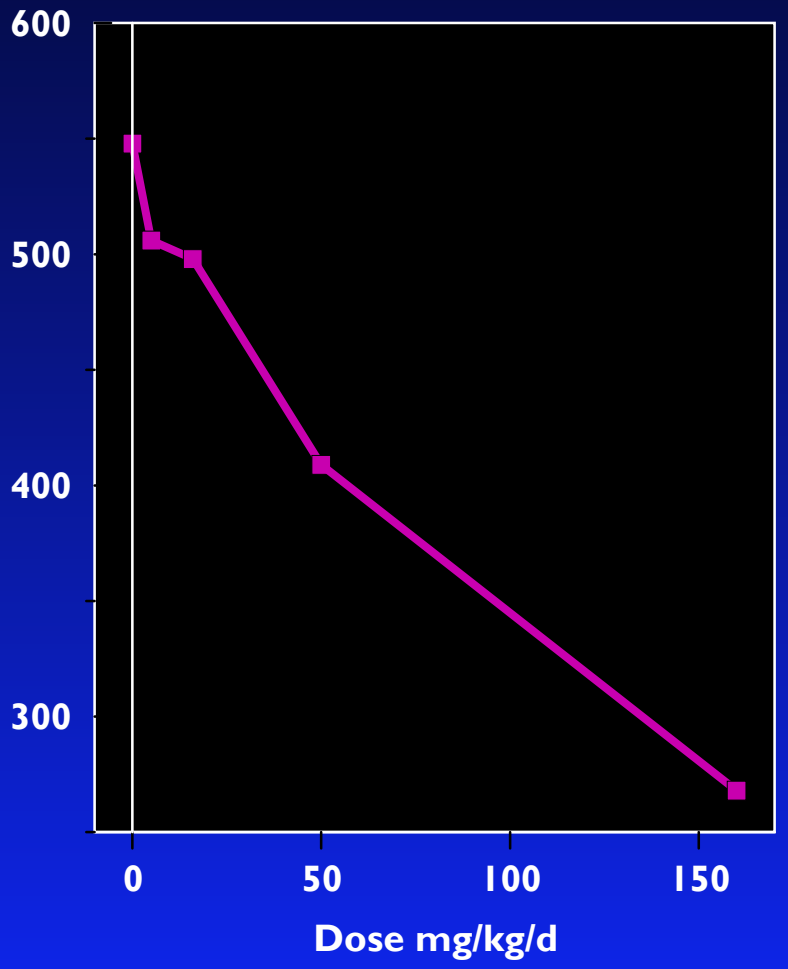
84. Effect of p,p' DDE on Seminal Vesicle weights. Data from four labs



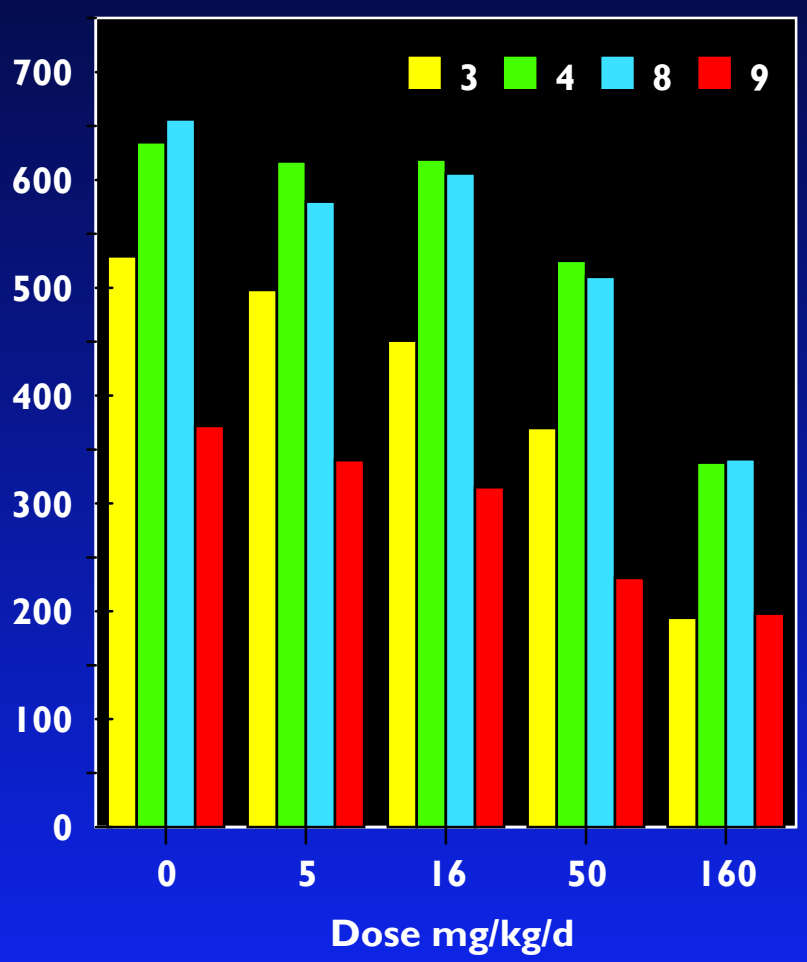


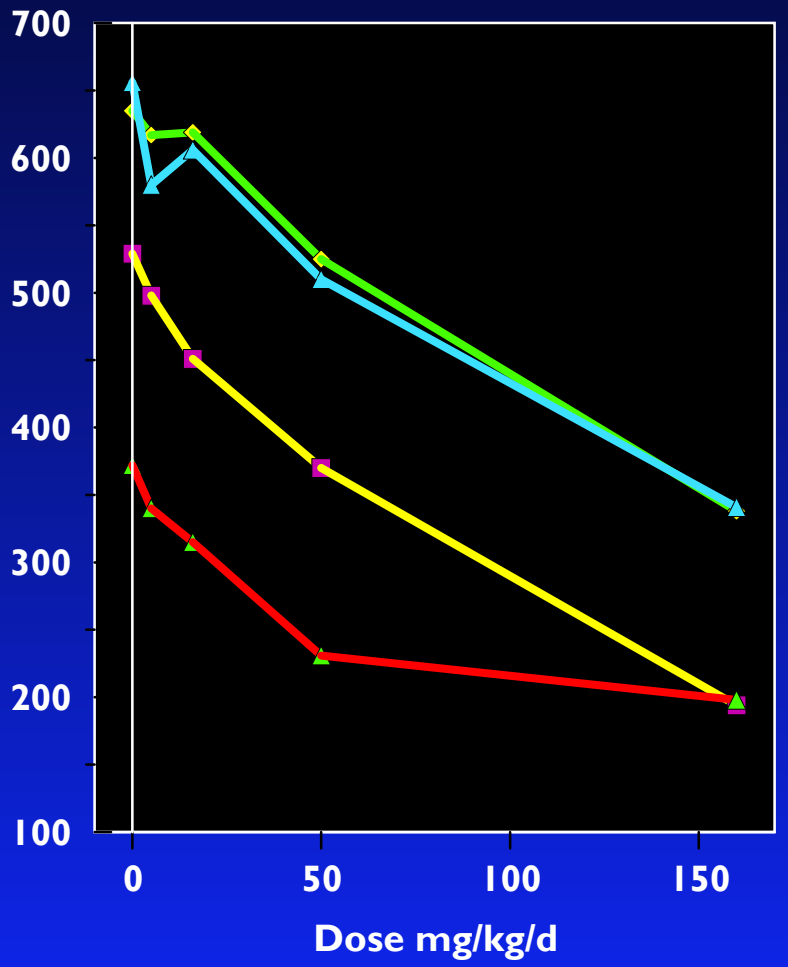
85. Effect of p,p' DDE on LABC weights. Data from four labs



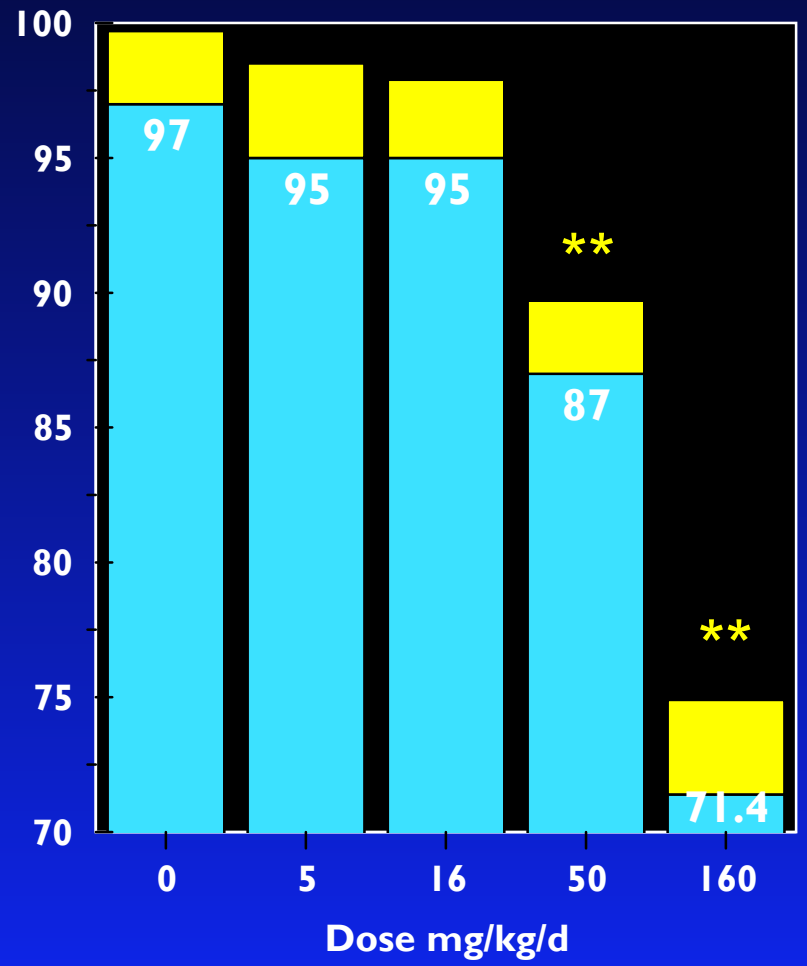


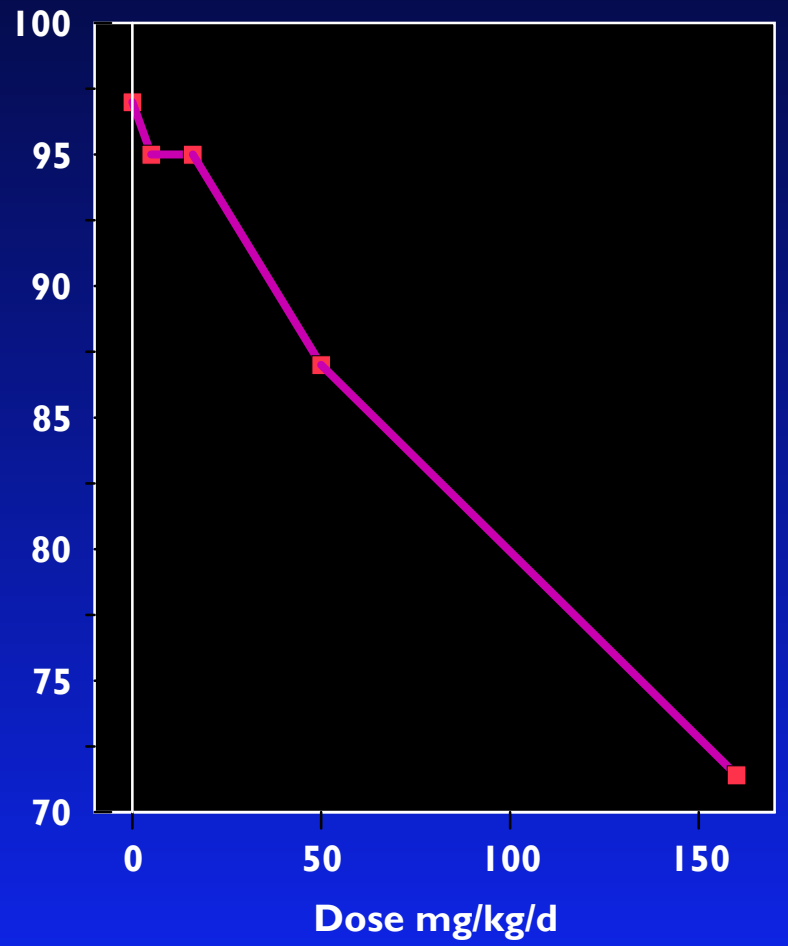
86. Effect of p,p' DDE on LABC weights. Data from four labs



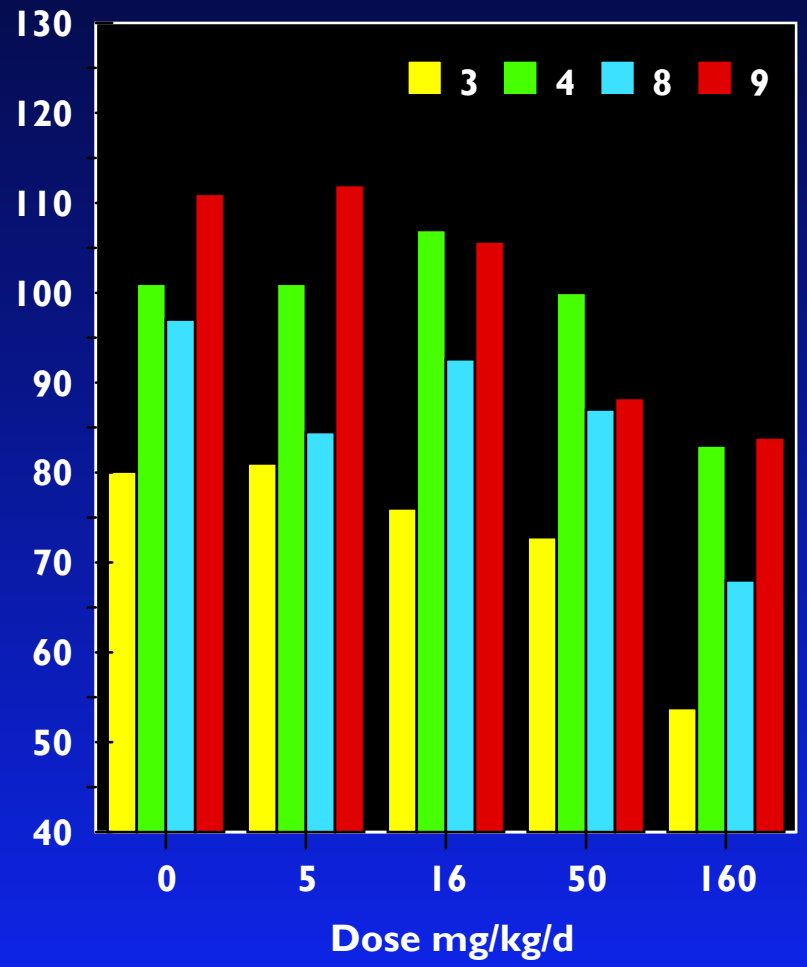


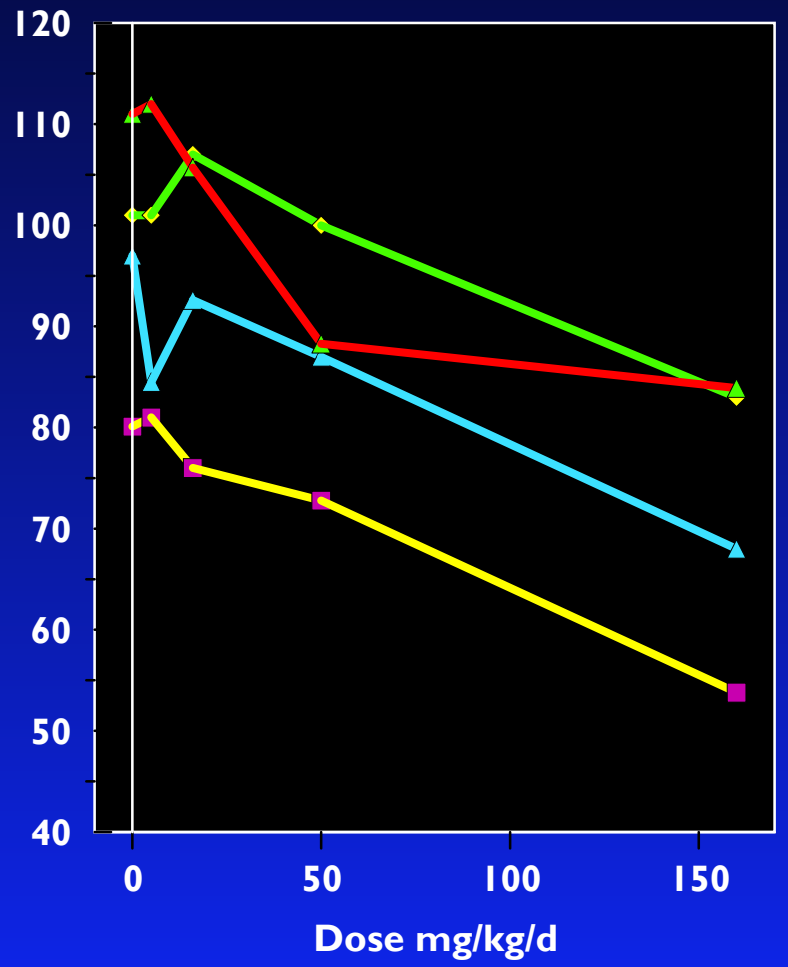
87. Effect of p,p' DDE on Glans penis weights. Data from four labs



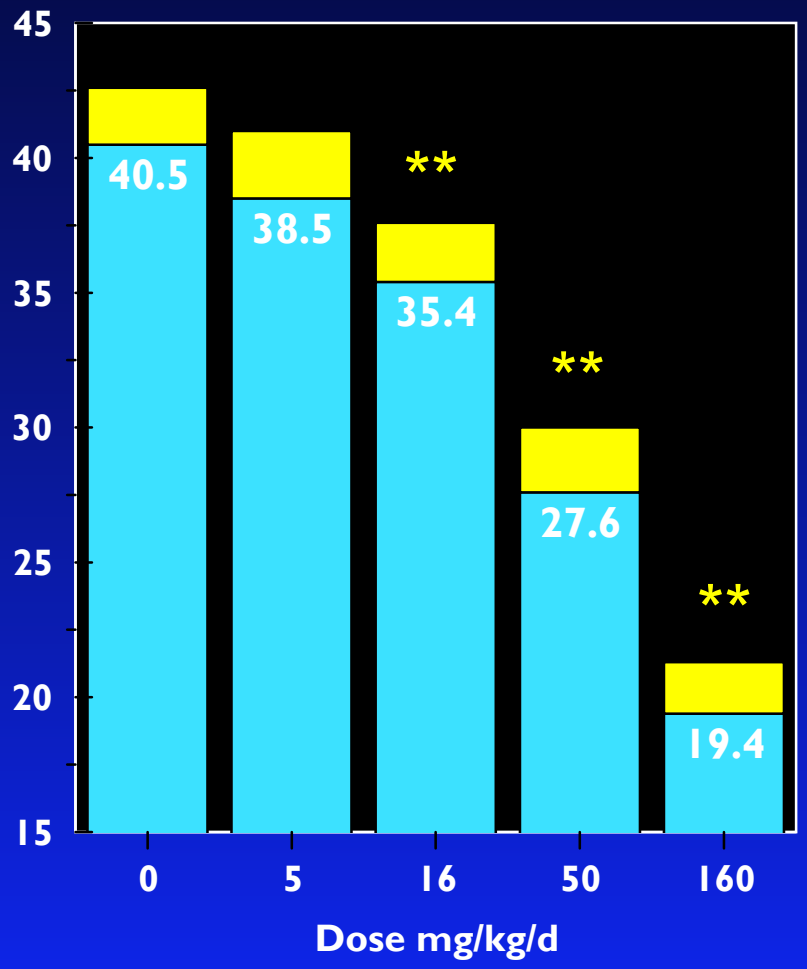


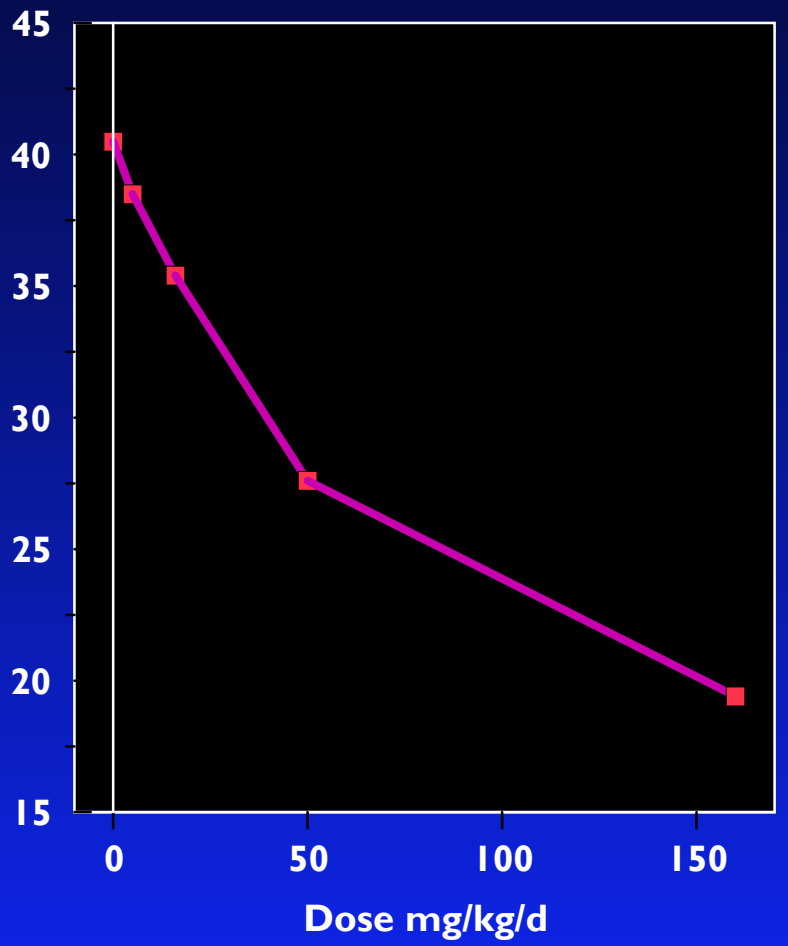
88. Effect of p,p' DDE on Glans Penis weights. Data from four labs



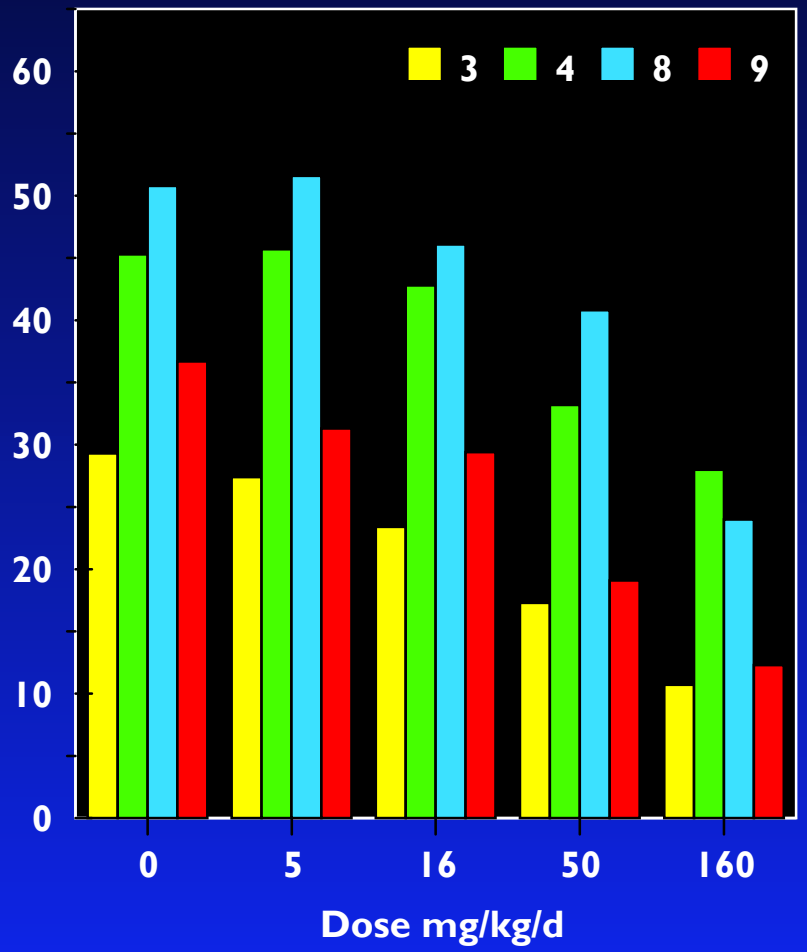


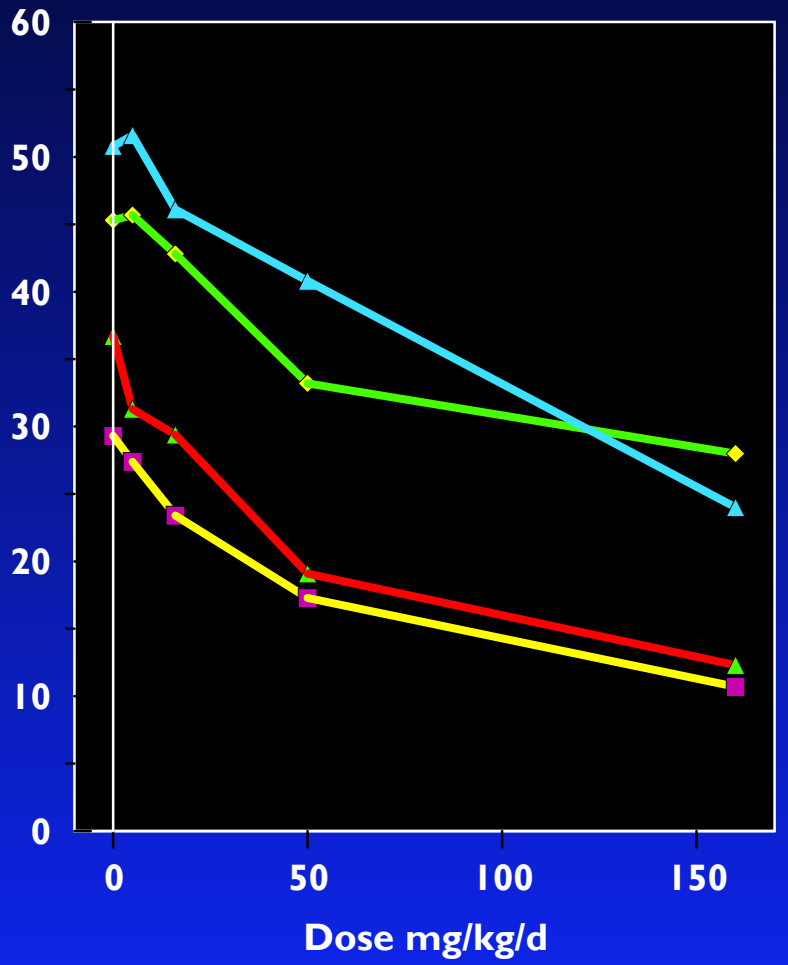
89. Effect of p,p' DDE on Cowper's gland weights. Data from four labs



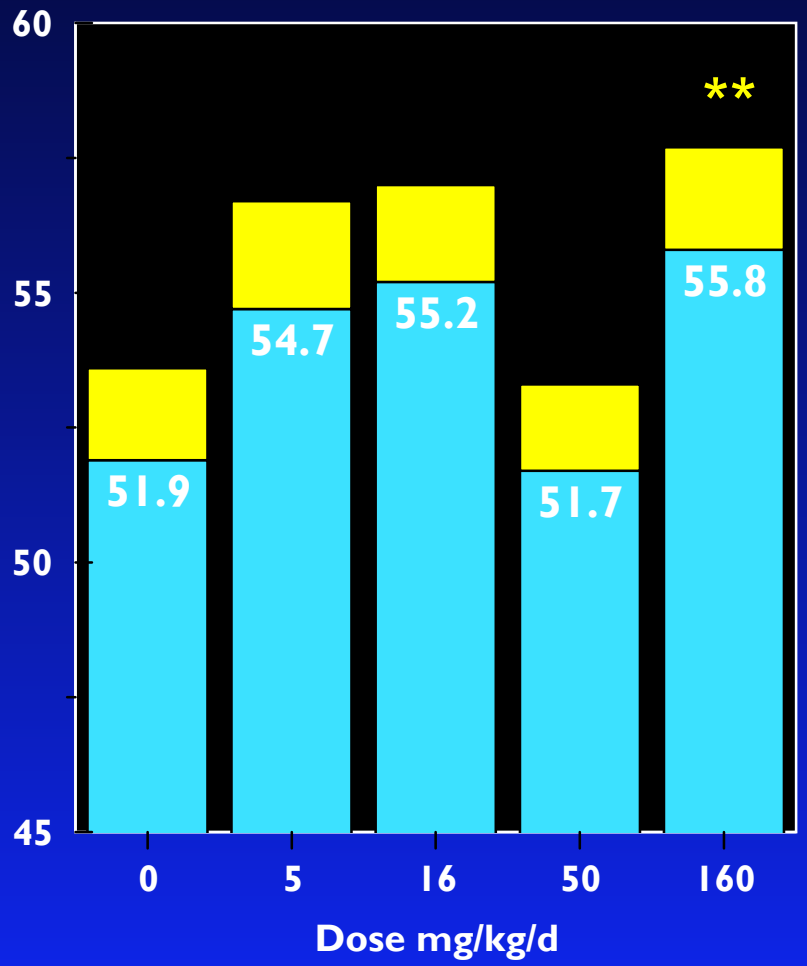


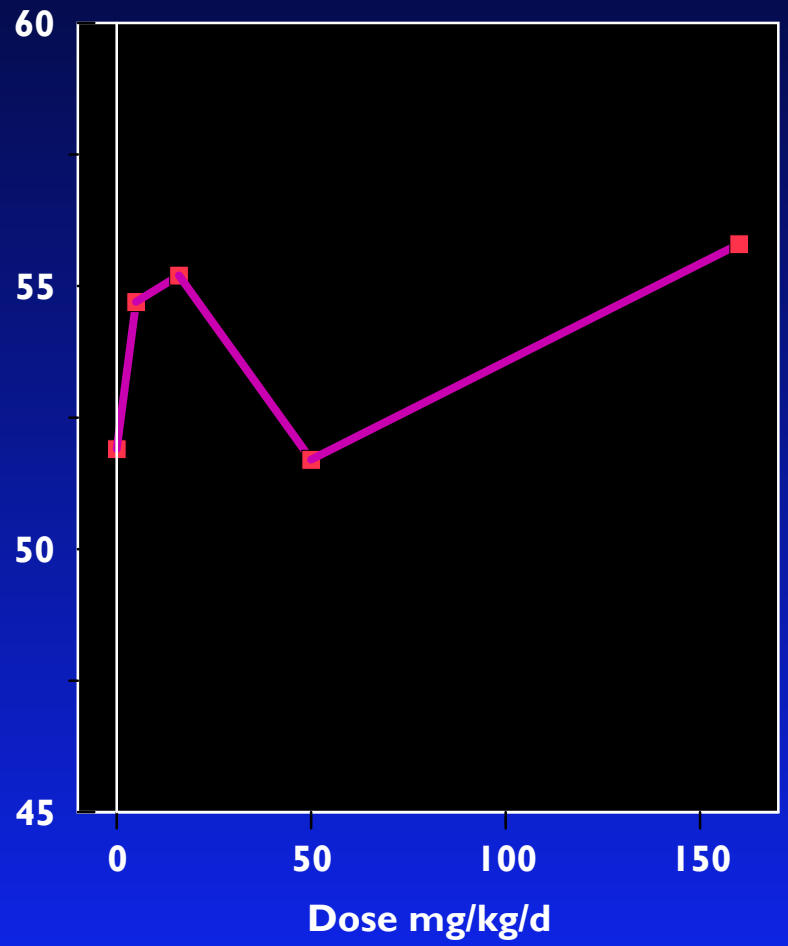
90. Effect of p,p' DDE on Cowper's gland weights. Data from four labs



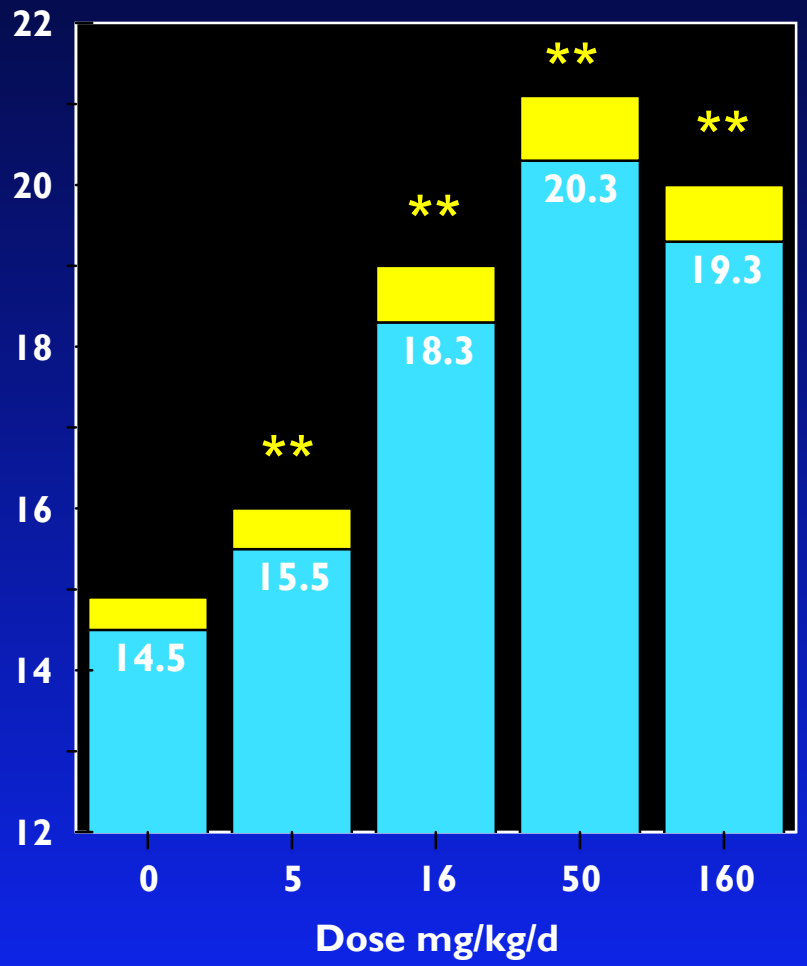


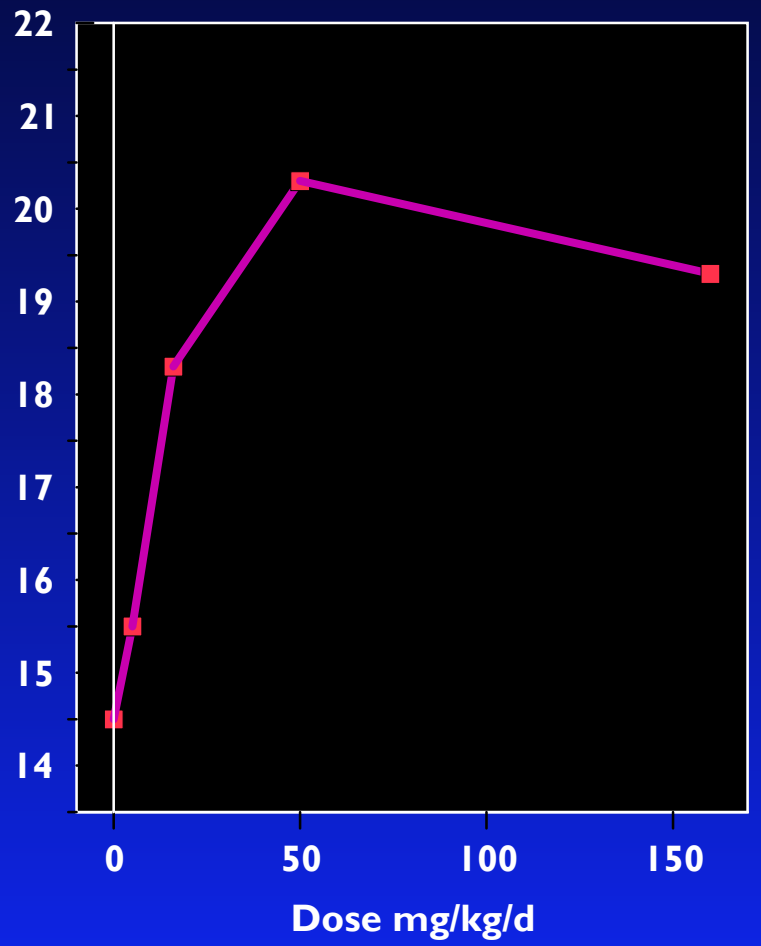
91. Effect of p,p' DDE on Adrenal weights. Data from four labs



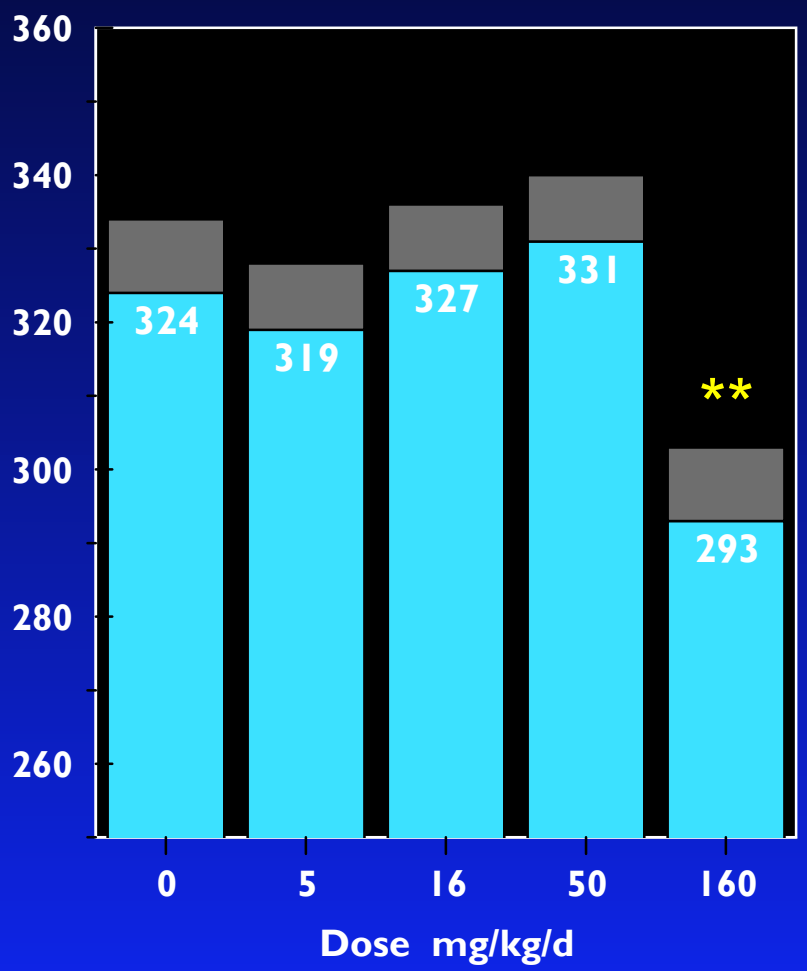


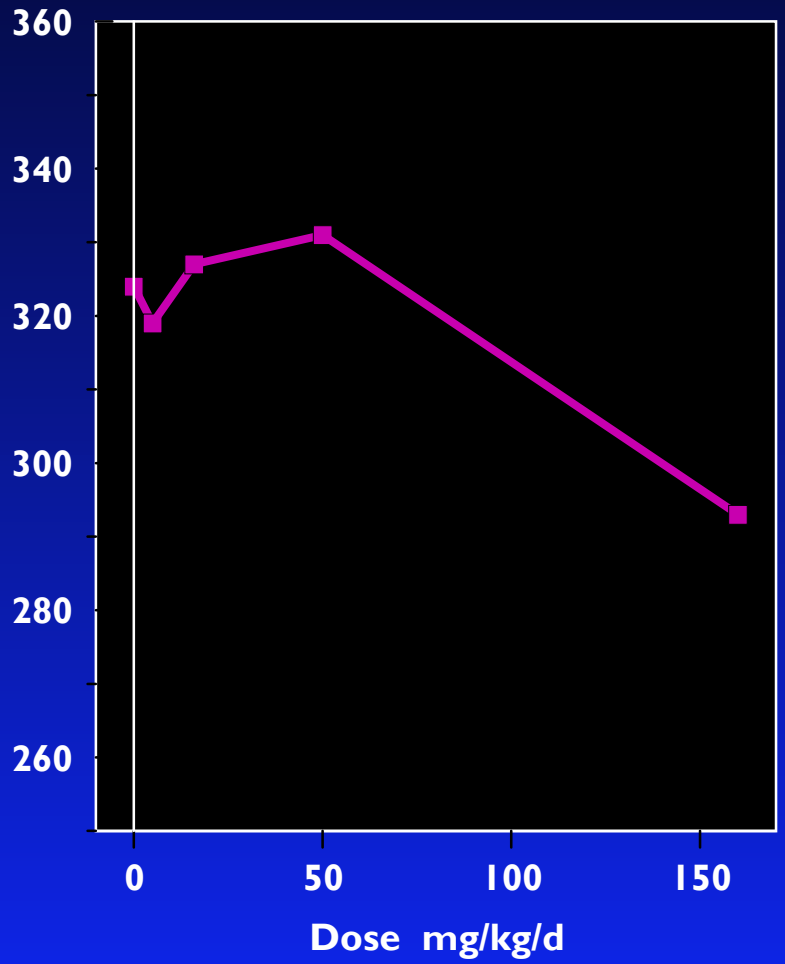
92. Effect of p,p' DDE on Liver weights. Data from four labs



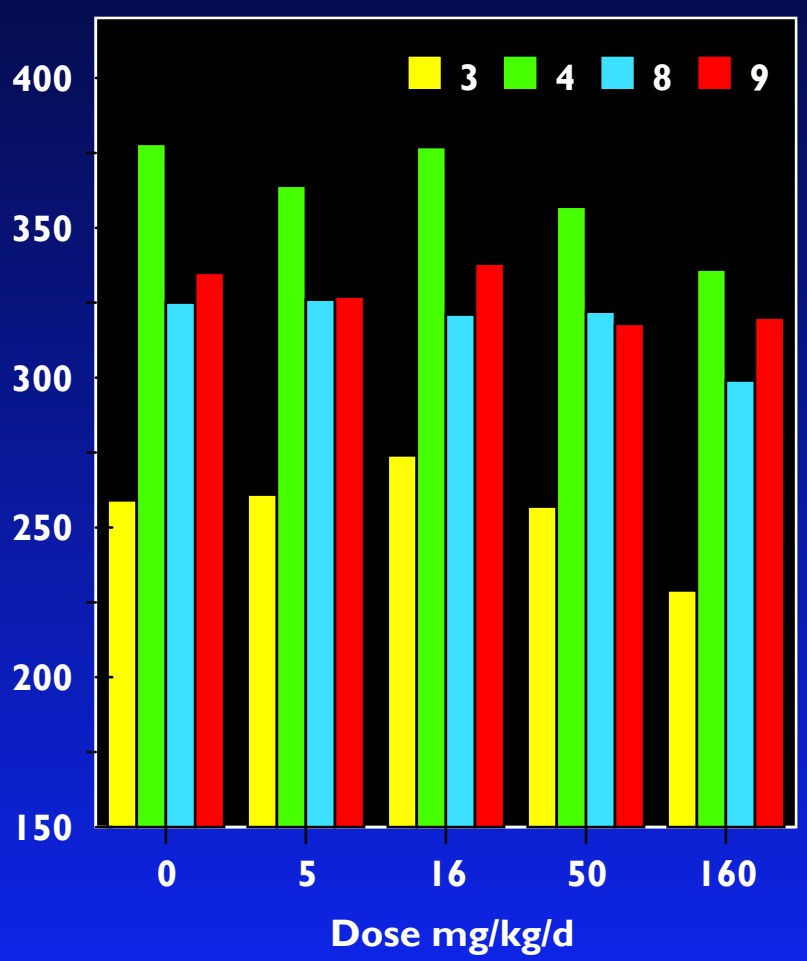


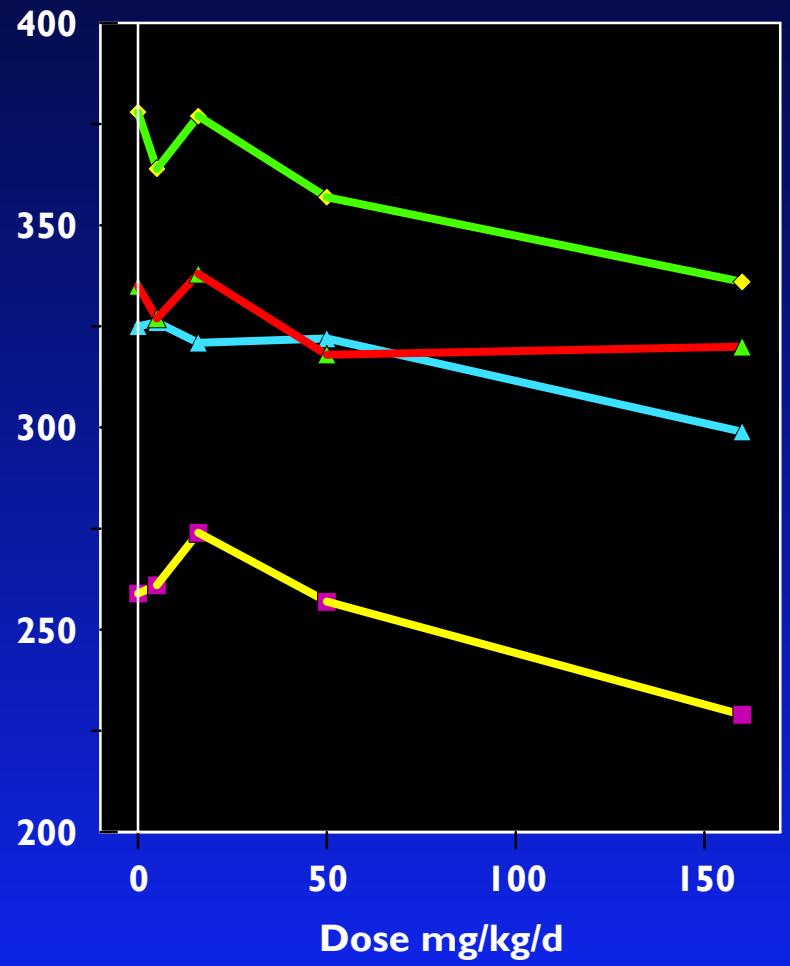
93. Effects of p,p' DDE on Body weight at necropsy





93 b. Effect of p,p' DDE on Body weights. Data from four labs

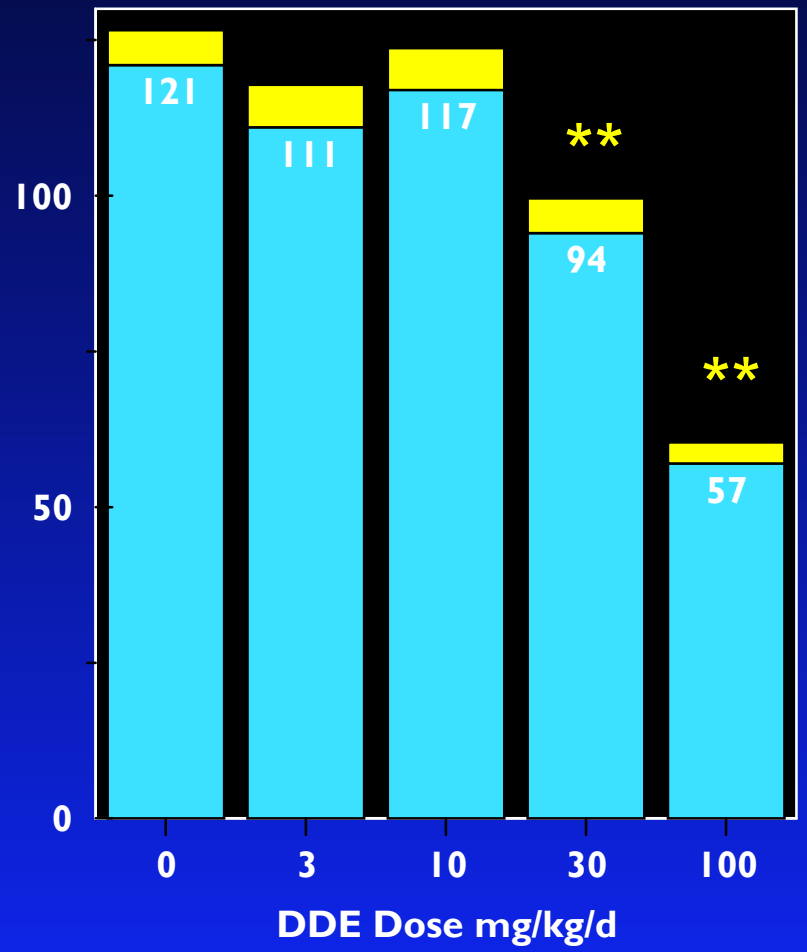


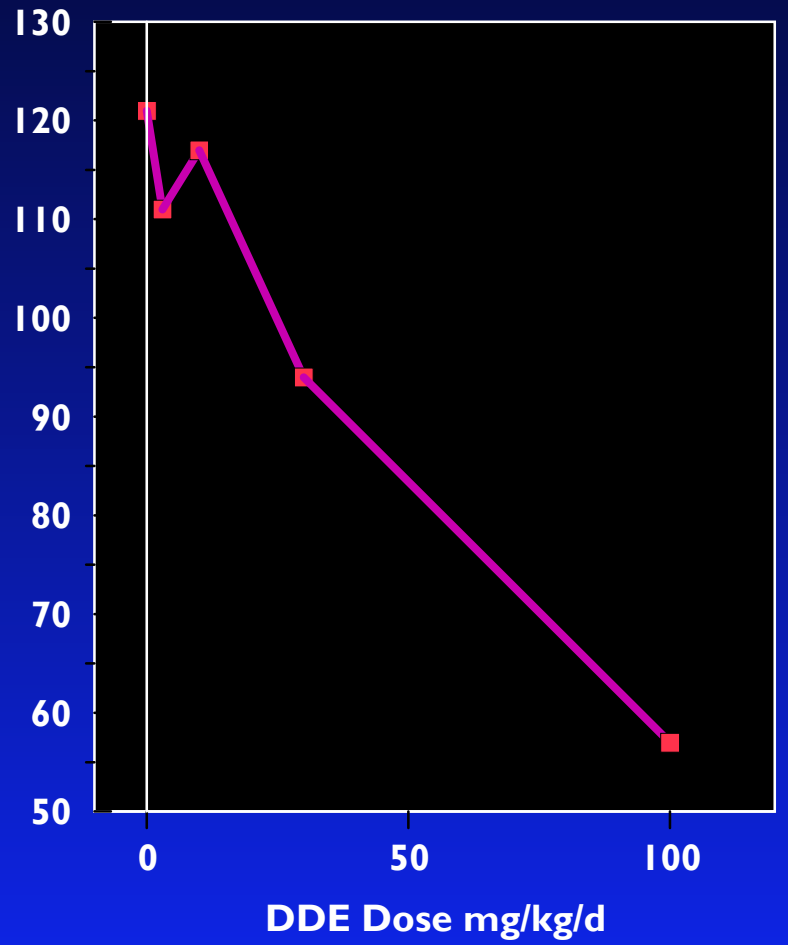


Hershberger Assay Interlaboratory study

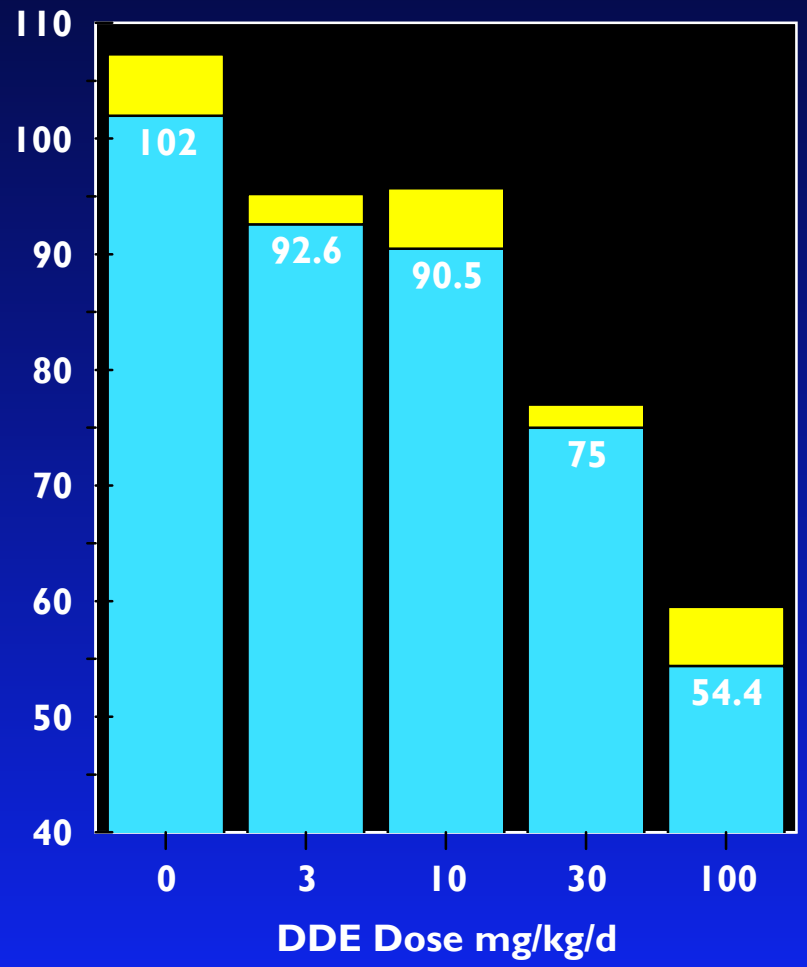
Japanese labs using DDE,
Jan 2003

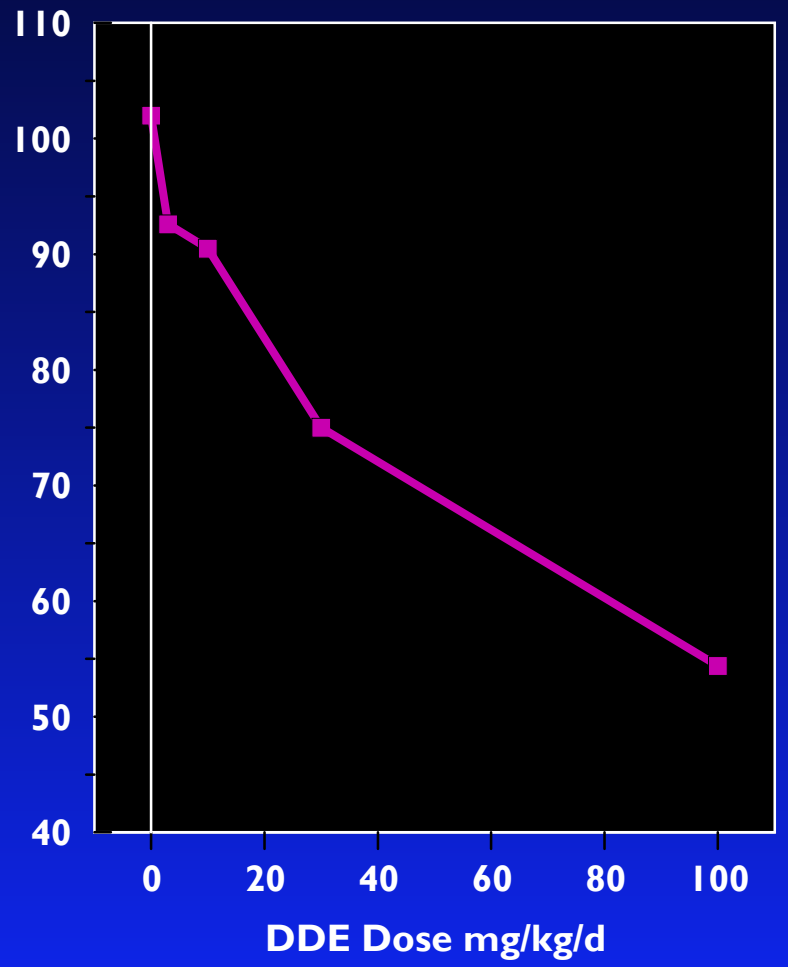
94. Effect of p,p' DDE on Ventral Prostate weights. Data from five labs



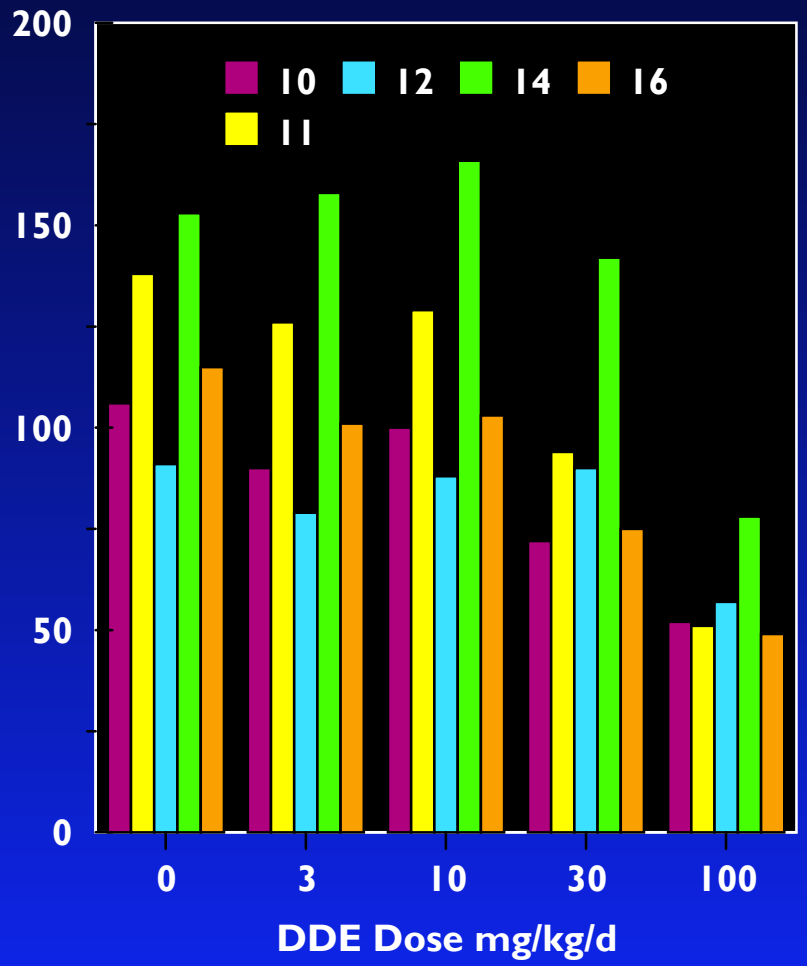


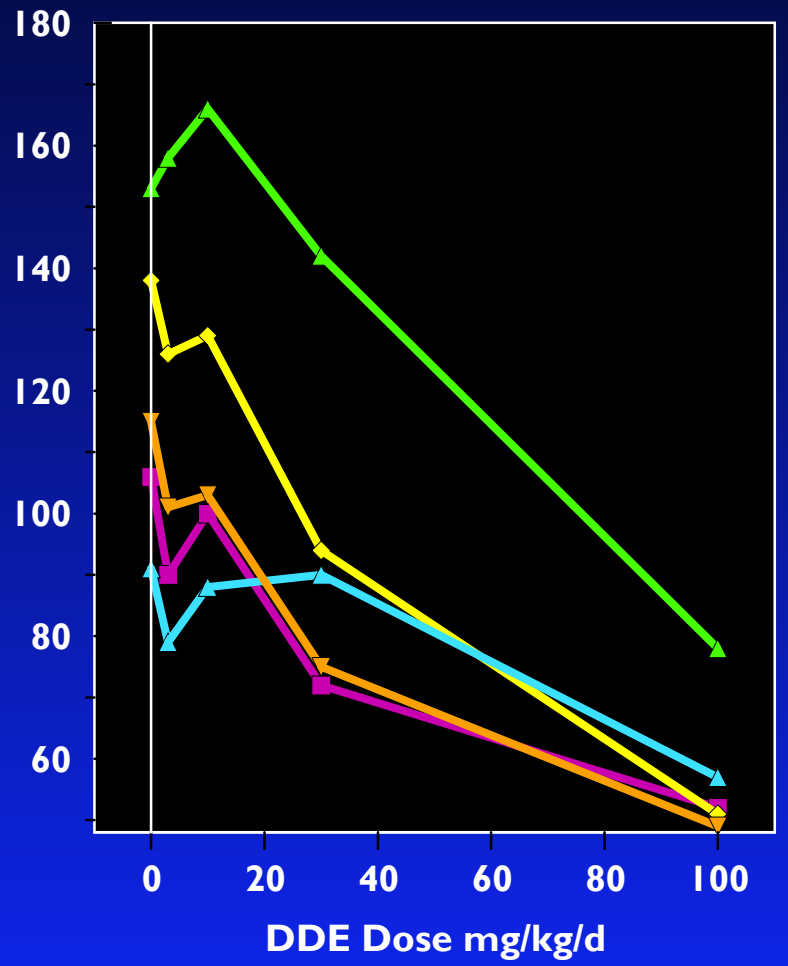
94b. Effect of p,p' DDE on dorsolateral prostate weight. Data from one lab



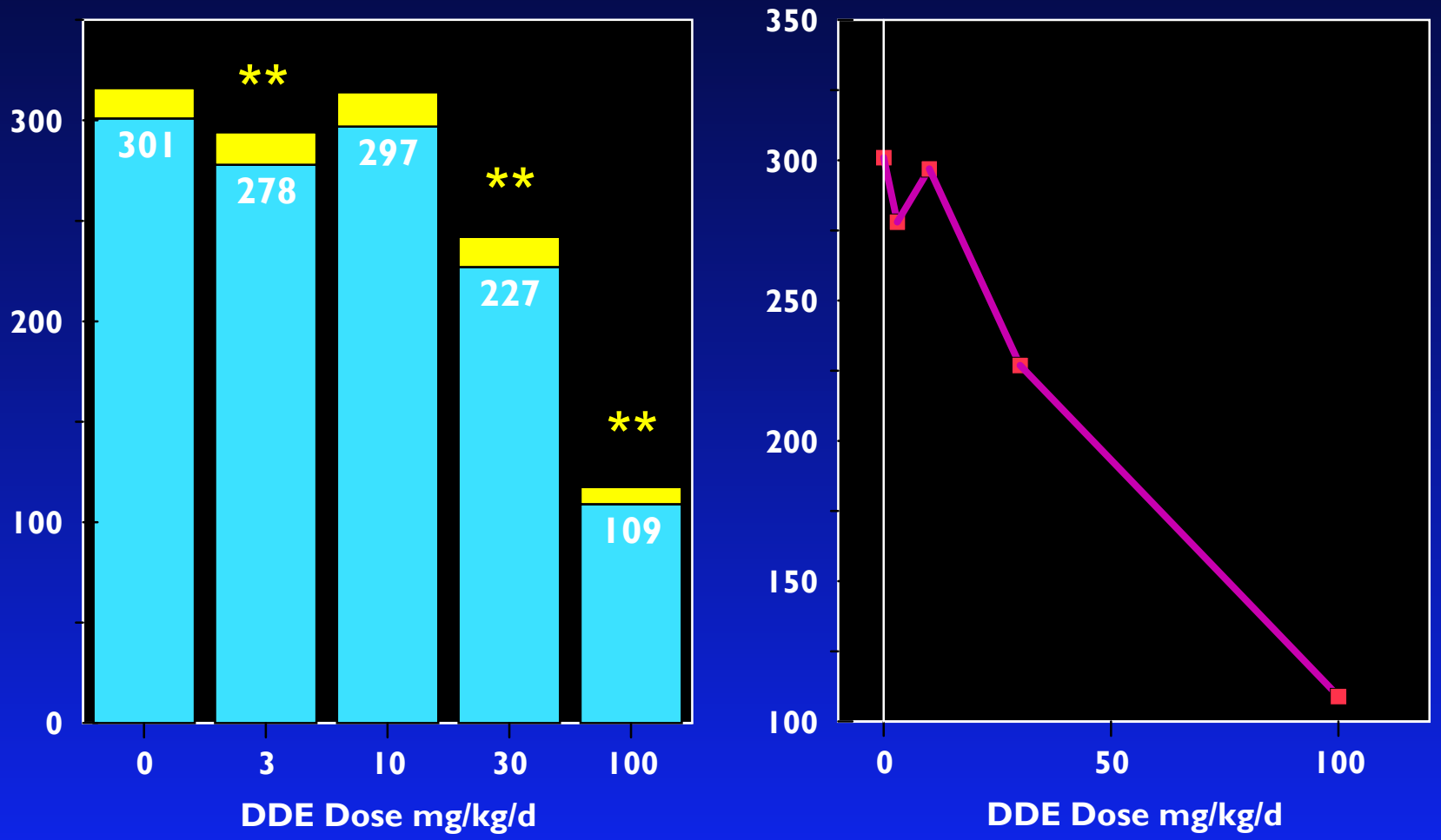


95. Effect of p,p' DDE on Ventral Prostate weights. Data from five labs

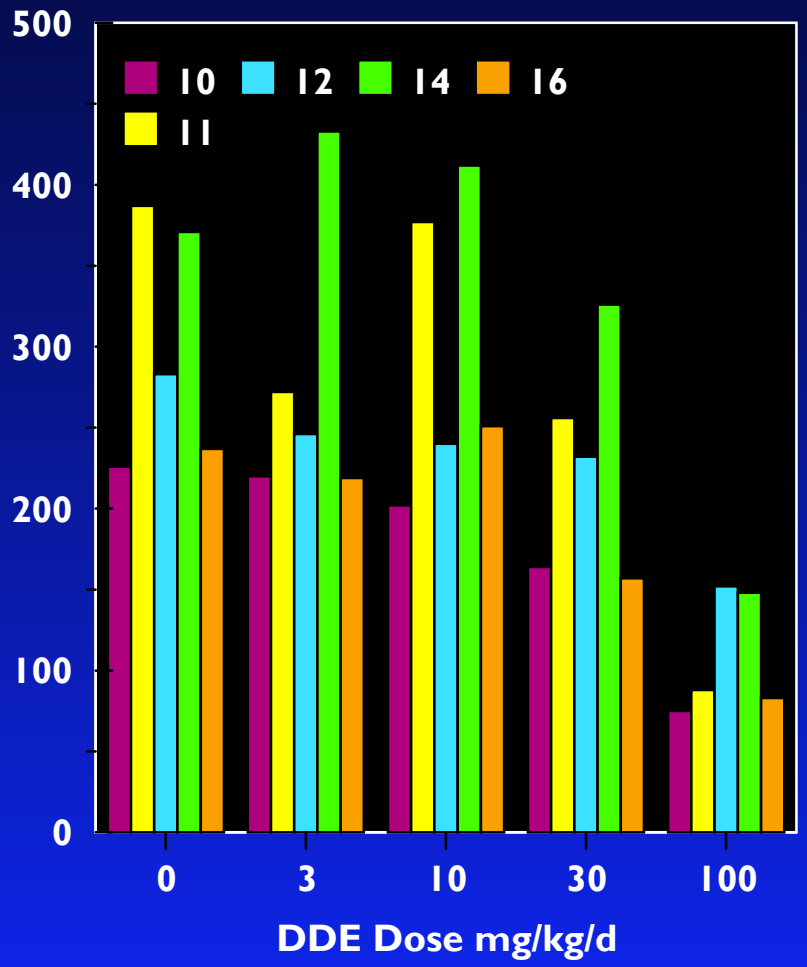


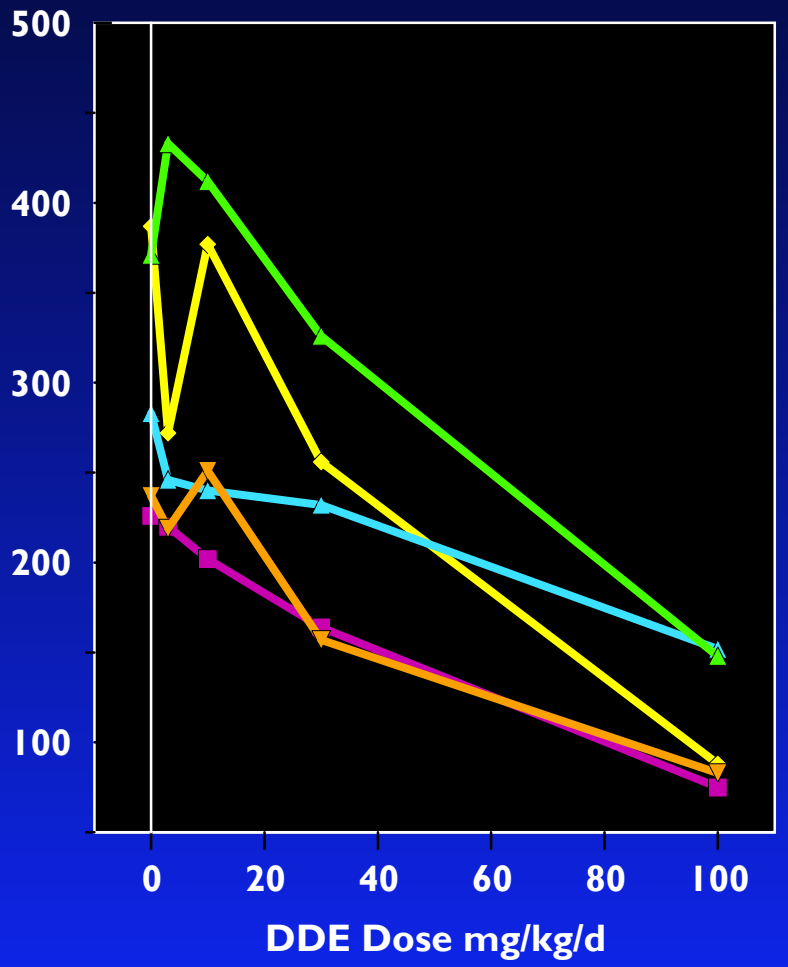


96. Effect of p,p' DDE on SV weights. Data from five labs

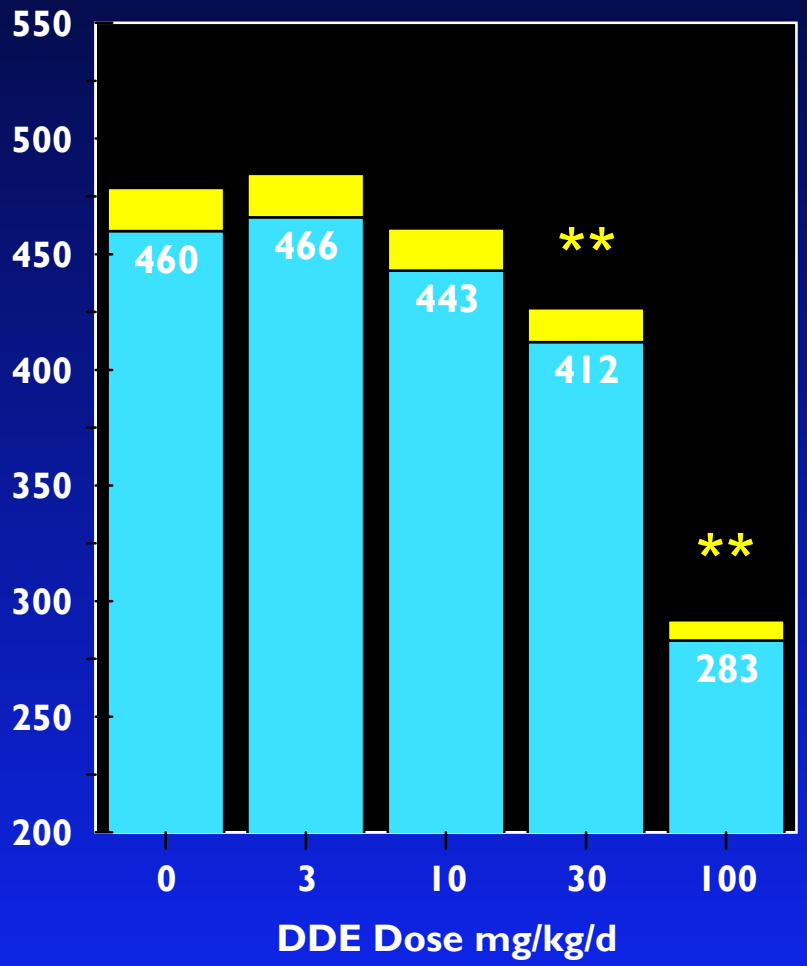


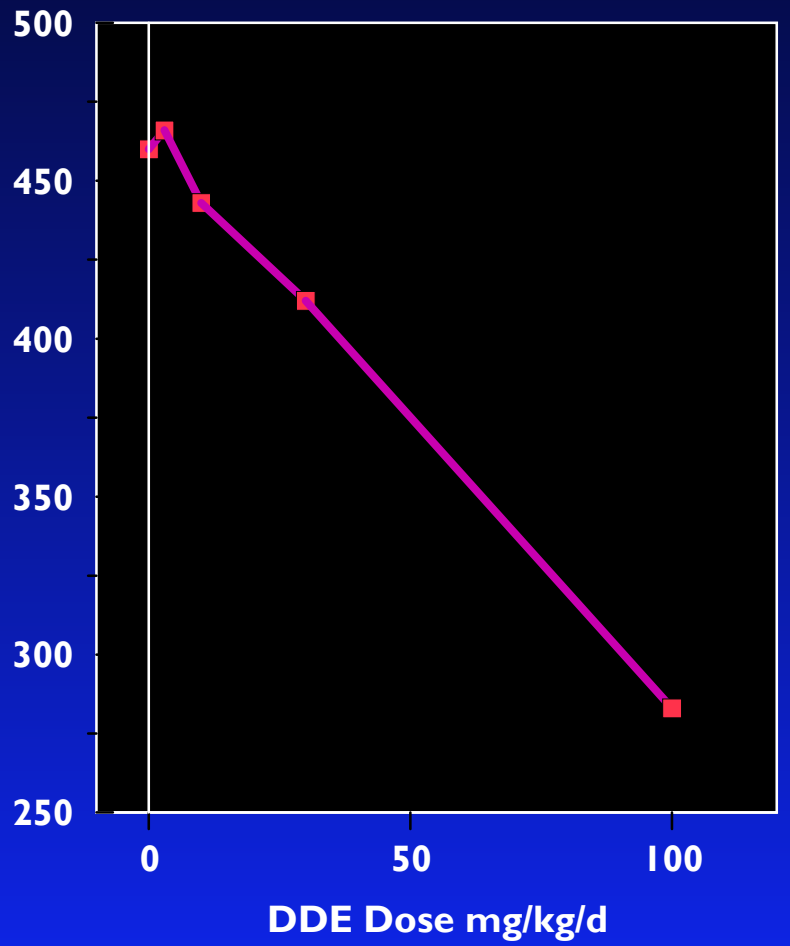
97. Effect of p,p' DDE on SV weights. Data from five labs



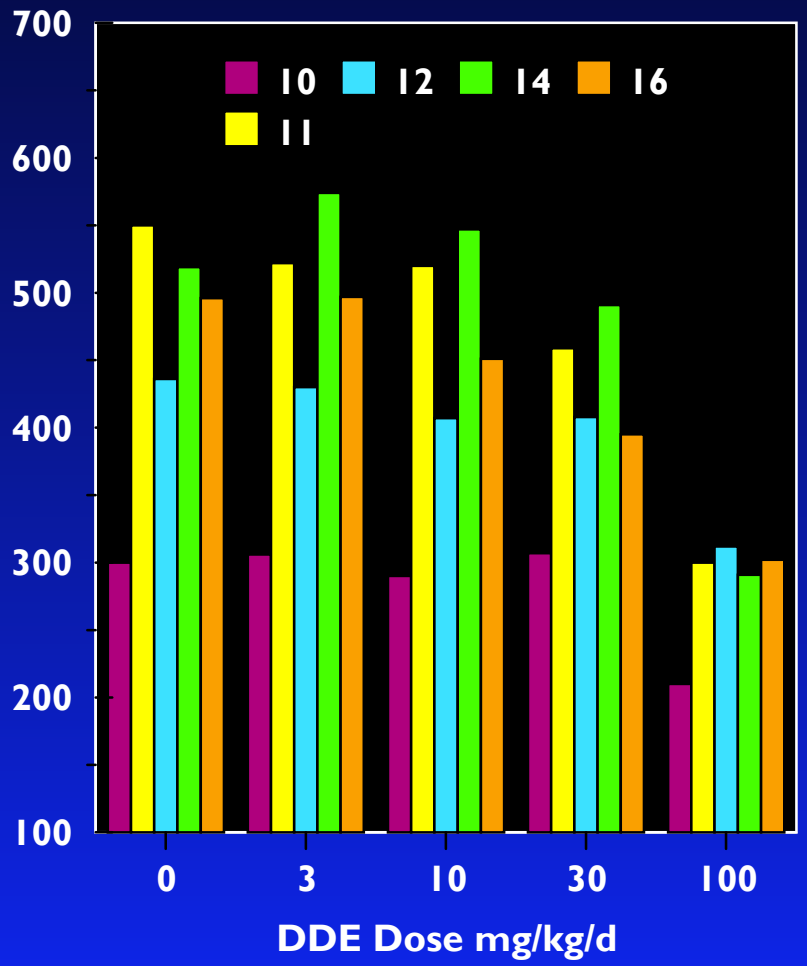


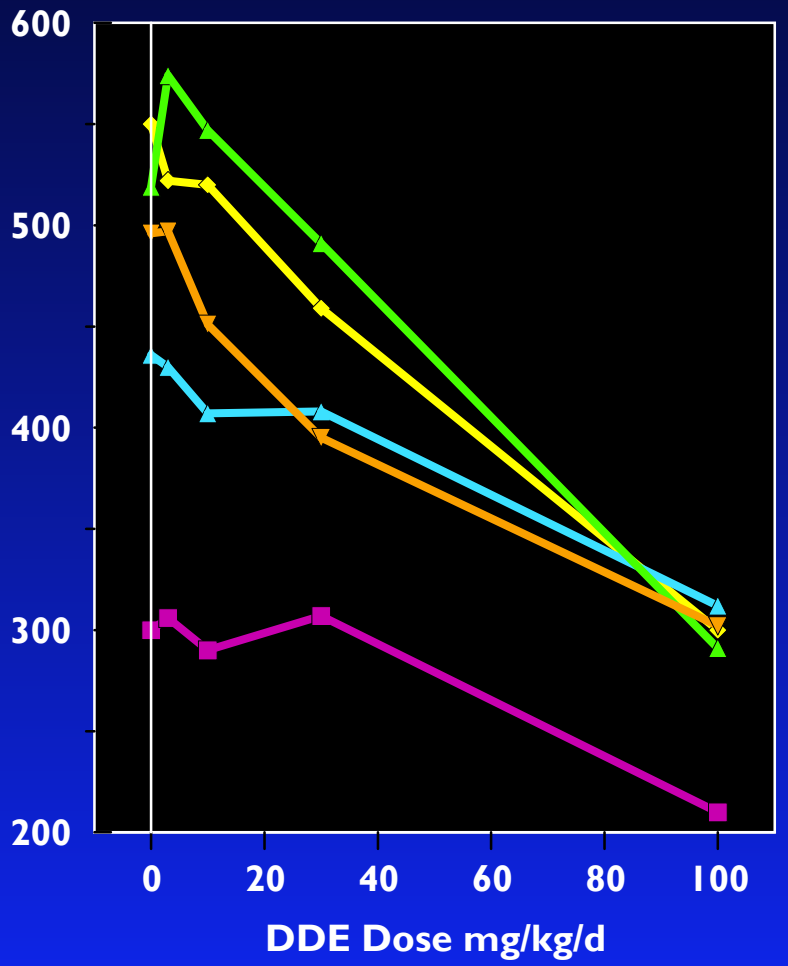
98. Effect of p,p' DDE on LABC weights. Data from five labs



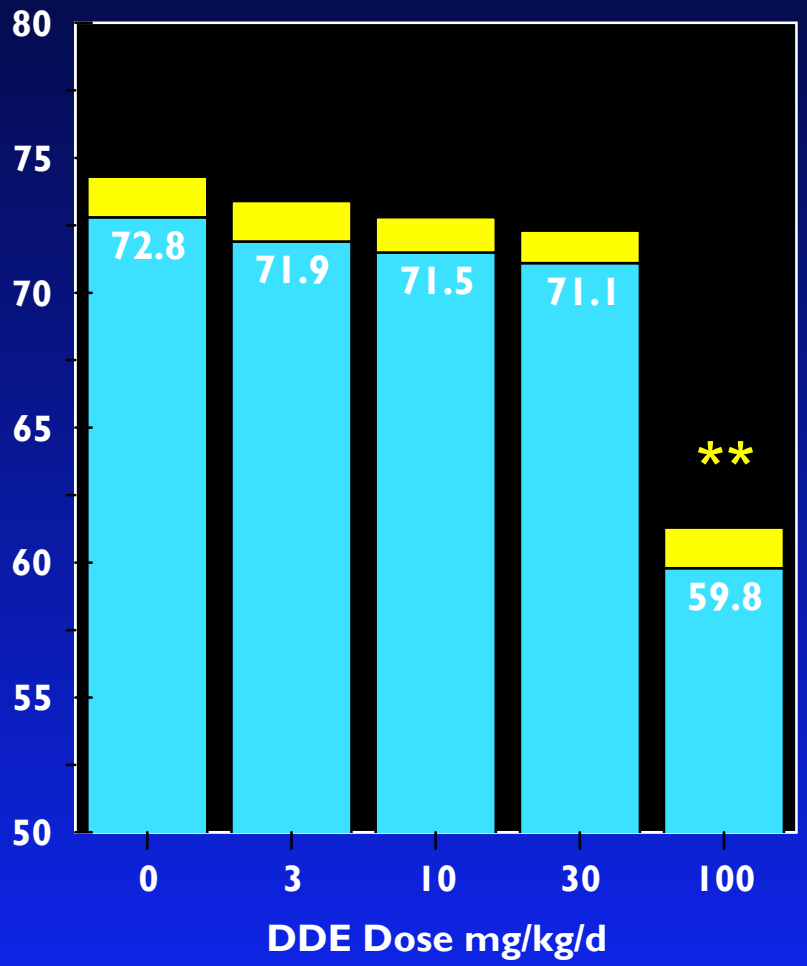


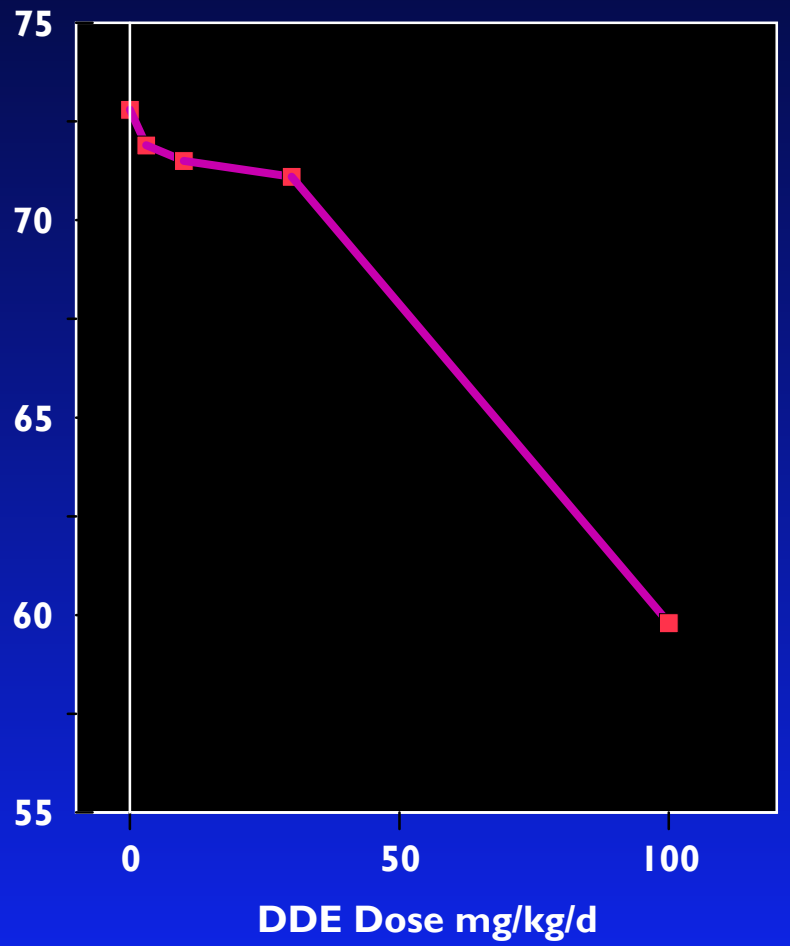
99. Effect of p,p' DDE on LABC weights. Data from five labs



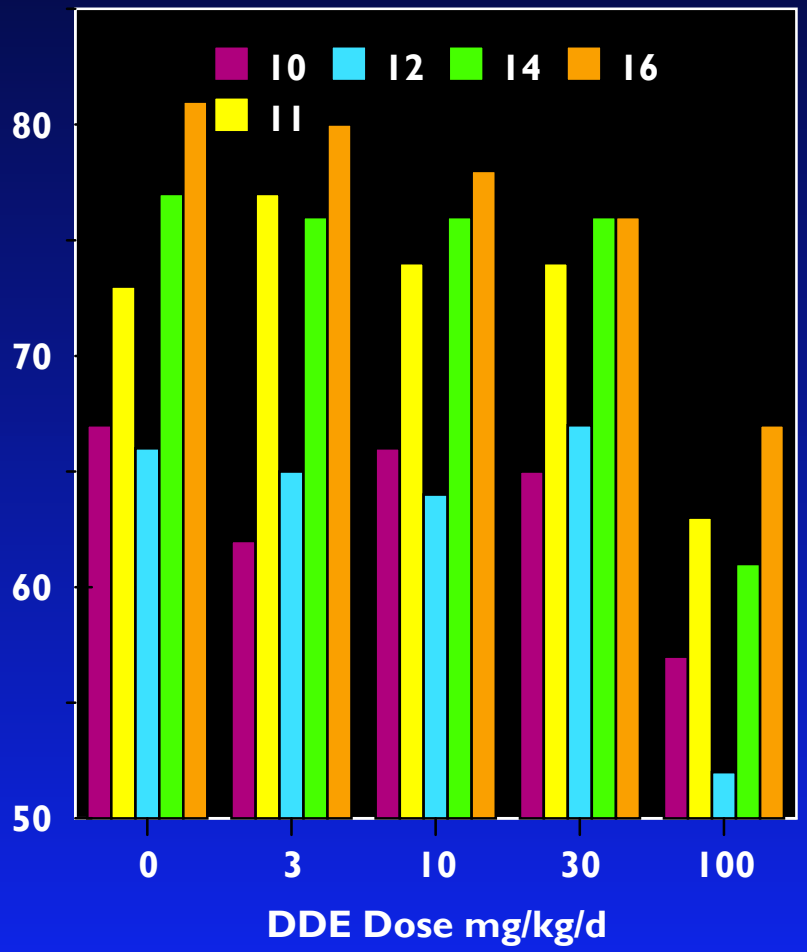


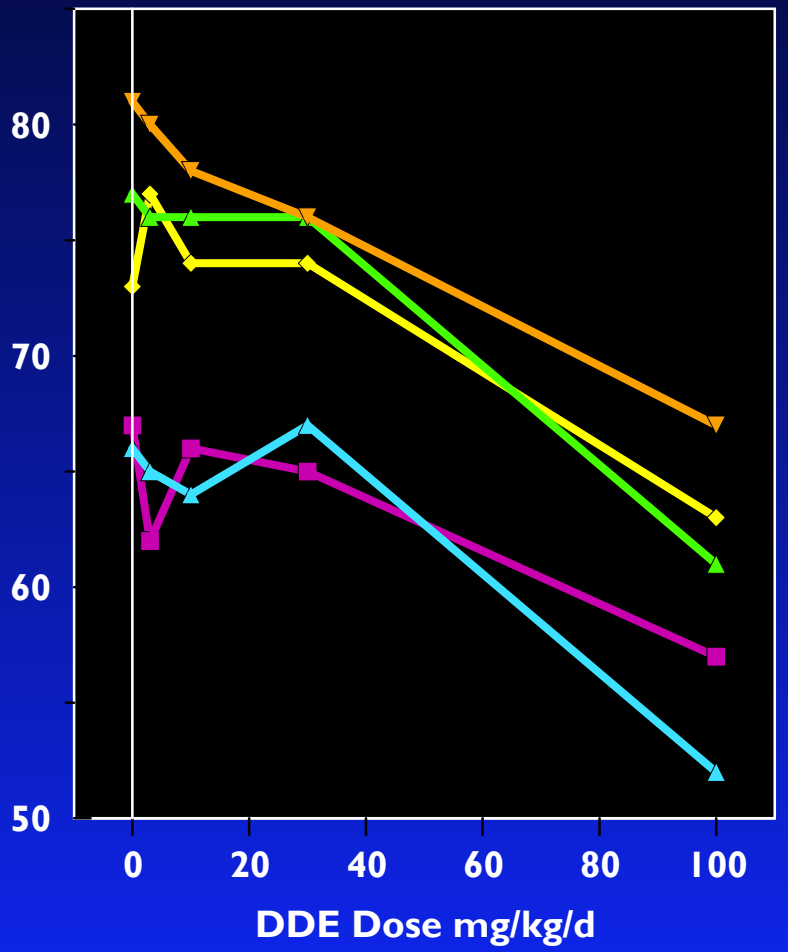
100. Effect of p,p' DDE on Glans Penis weights. Data from five labs



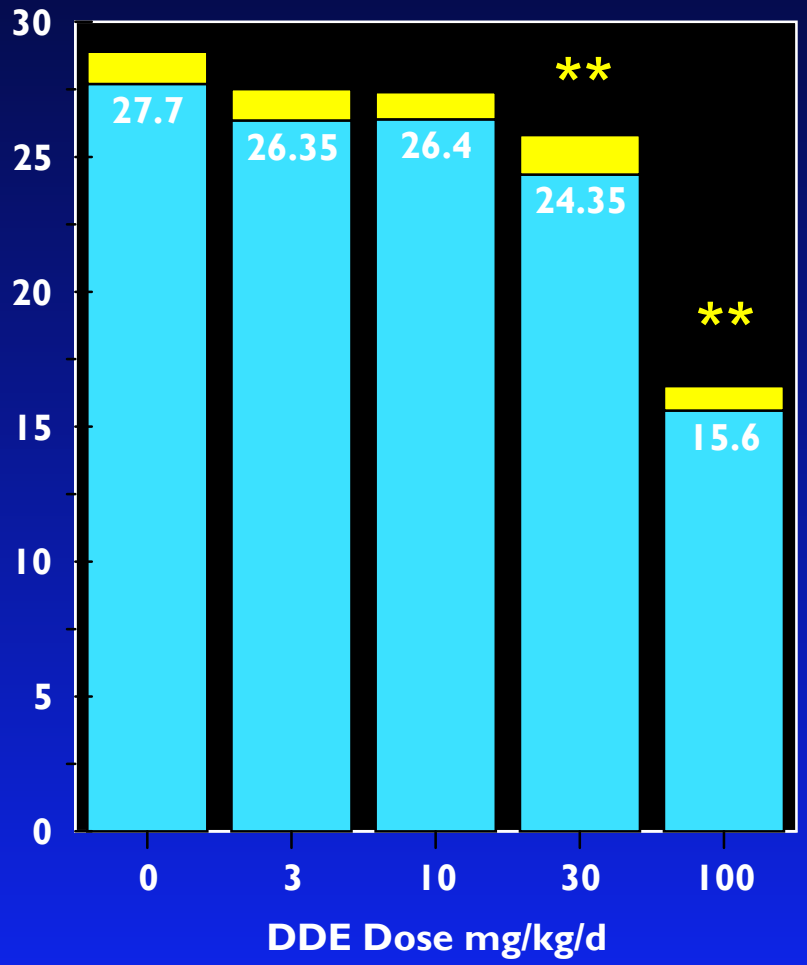


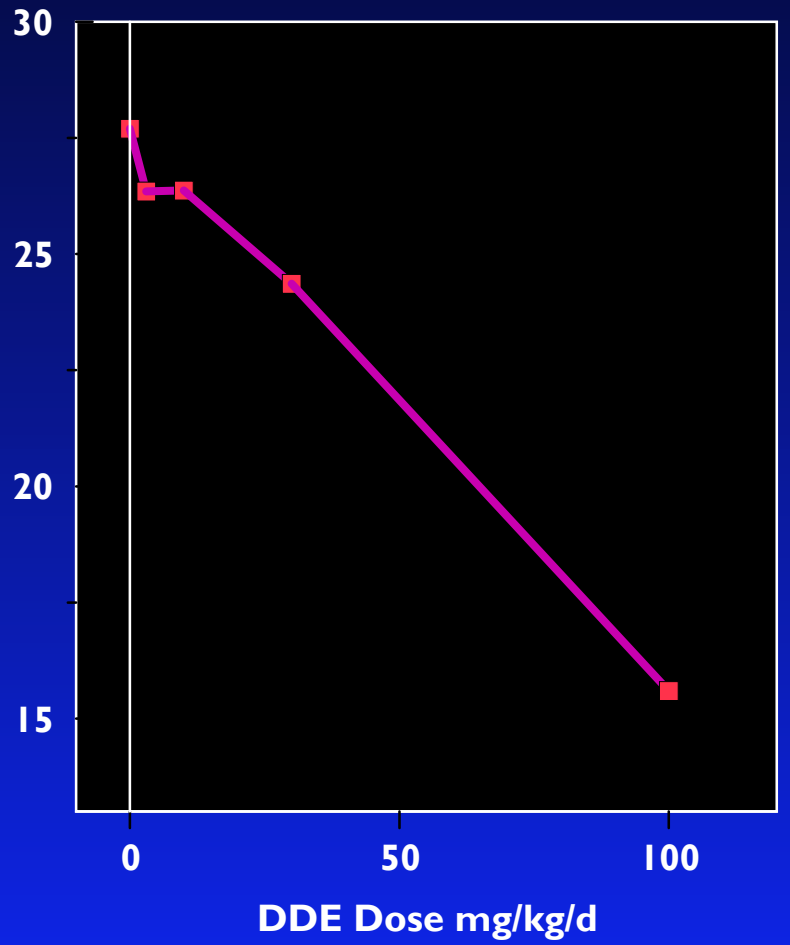
101. Effect of p,p' DDE on Glans Penis weights. Data from five labs



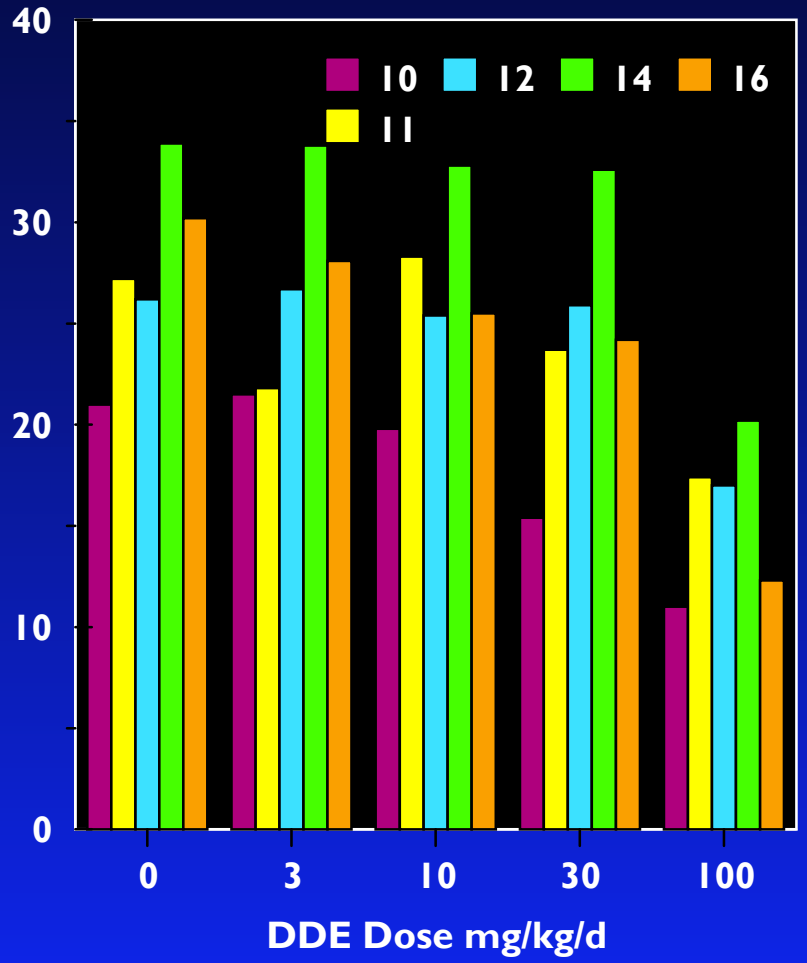


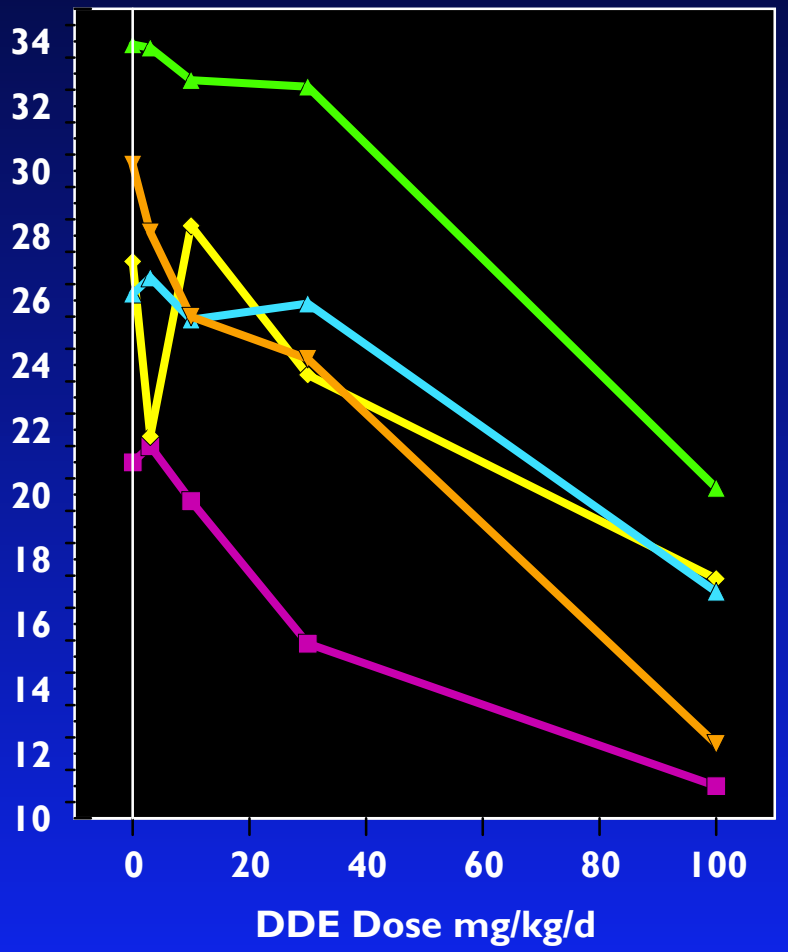
102. Effect of p,p' DDE on Cowper's gland weights. Data from five labs



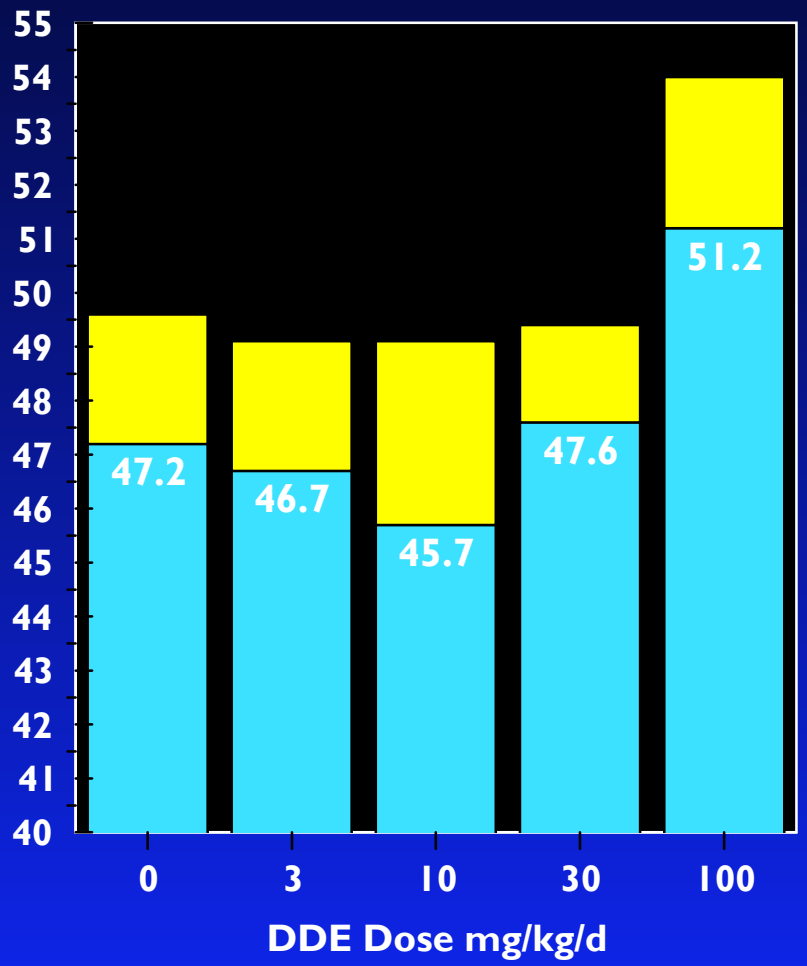


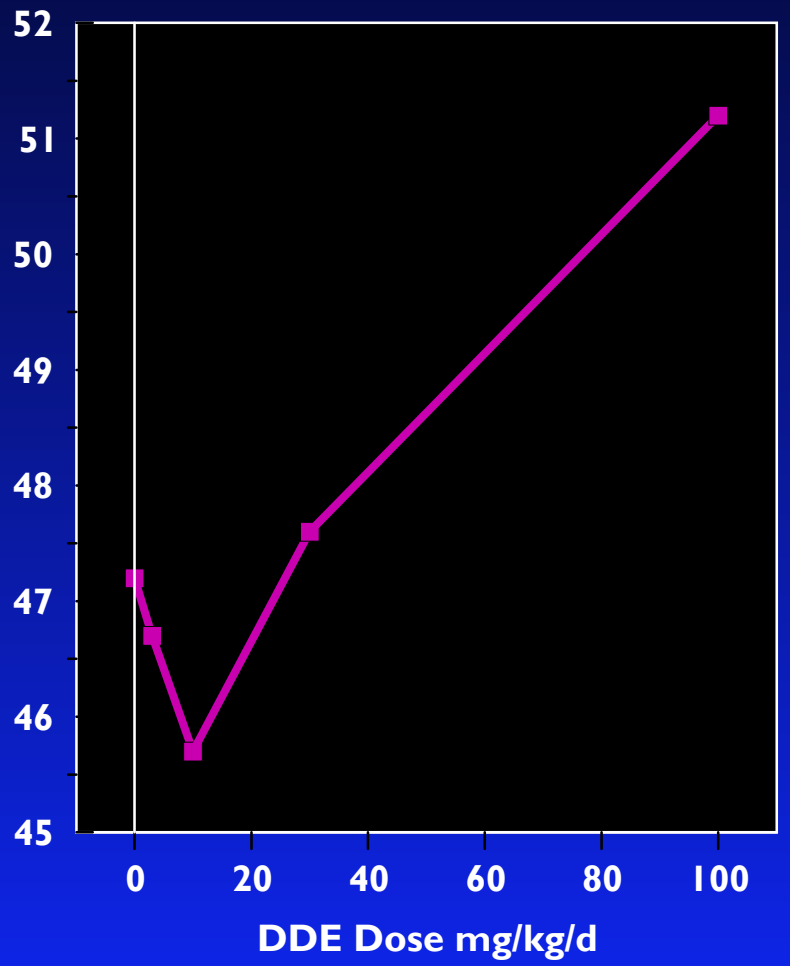
103. Effect of p,p' DDE on Cowper's gland weights. Data from five labs



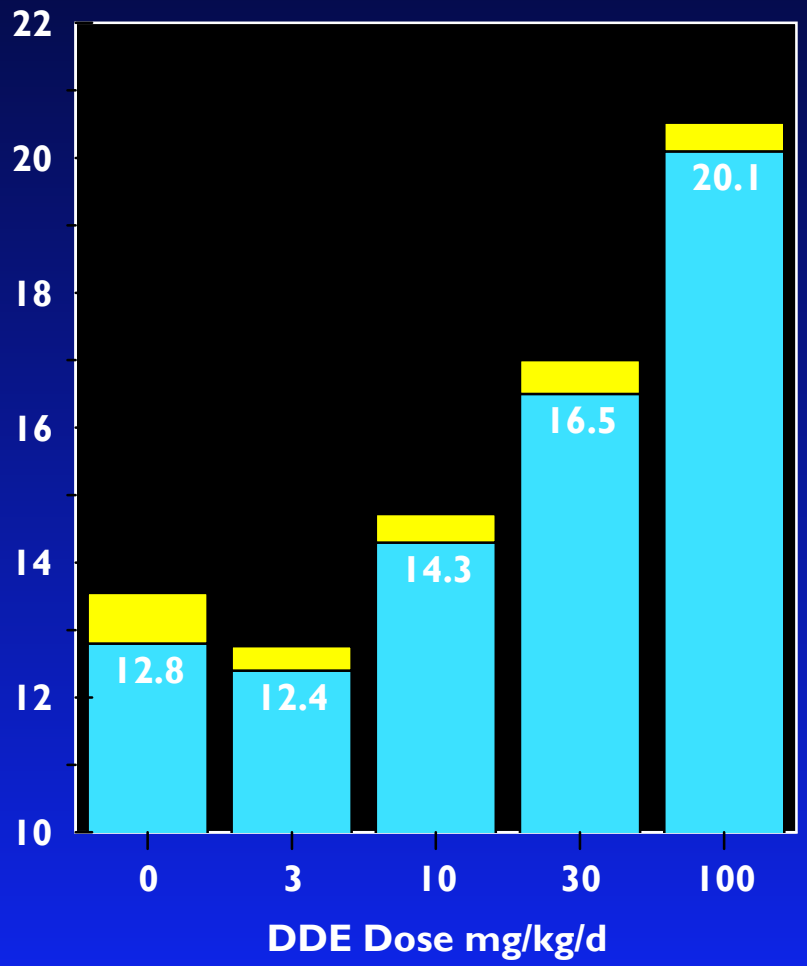


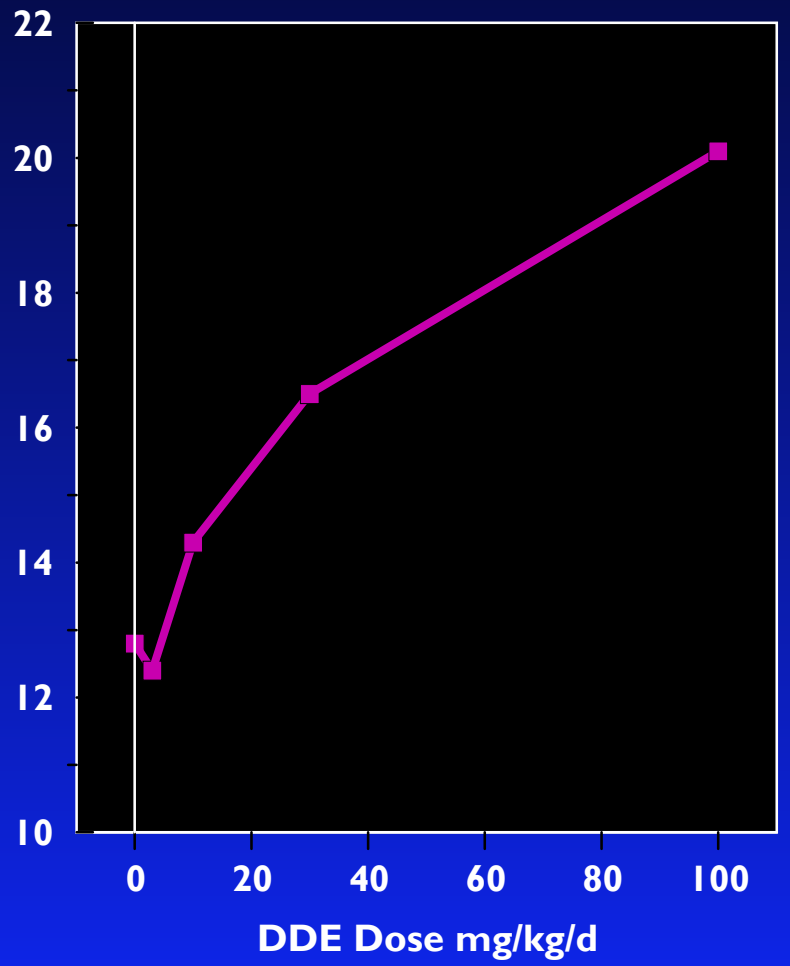
104. Effect of p,p' DDE on adrenal weights. Data from one lab



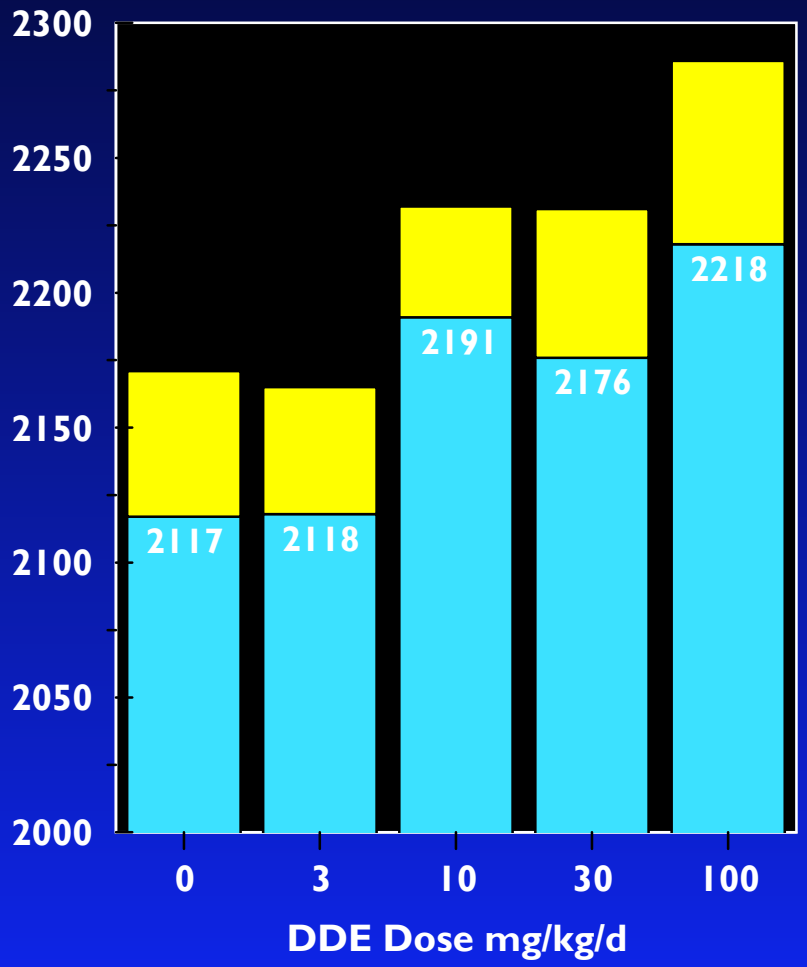


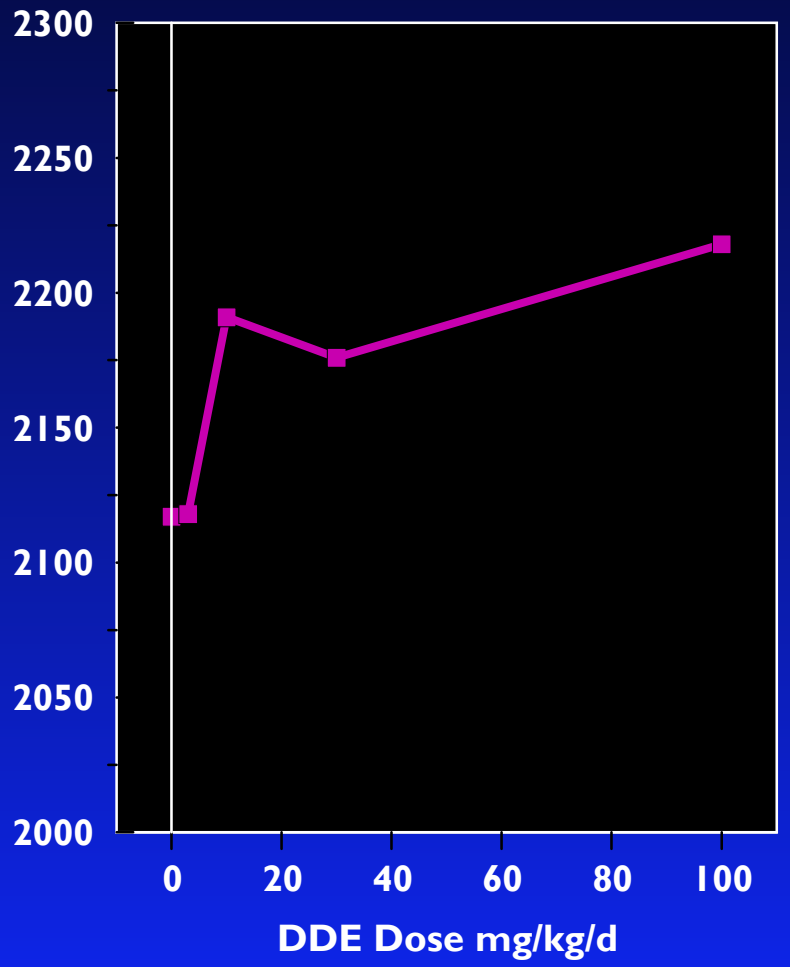
105. Effect of p,p' DDE on Liver weight gain. Data from one lab



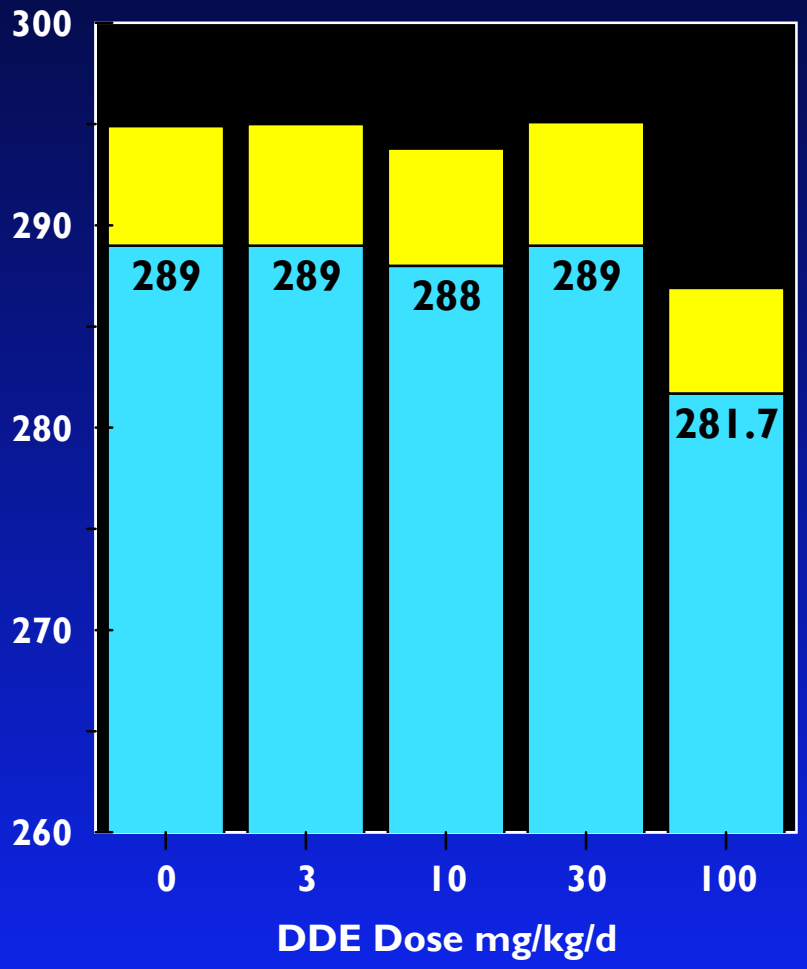


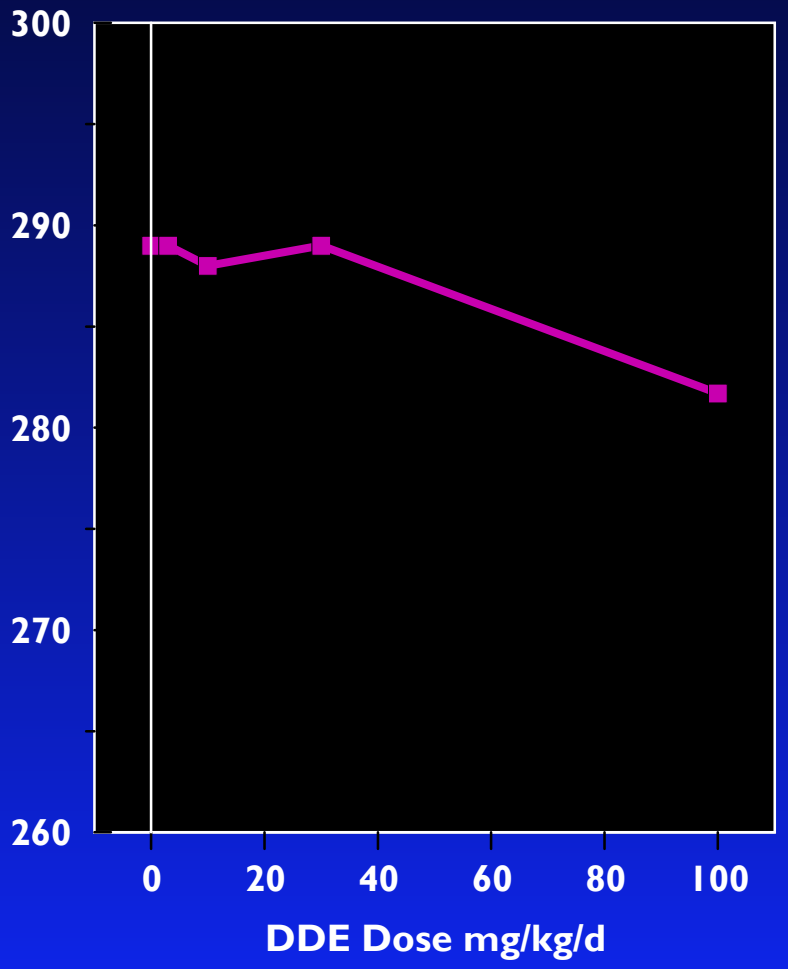
105b. Effect of p,p' DDE on kidney weights. Data from two labs



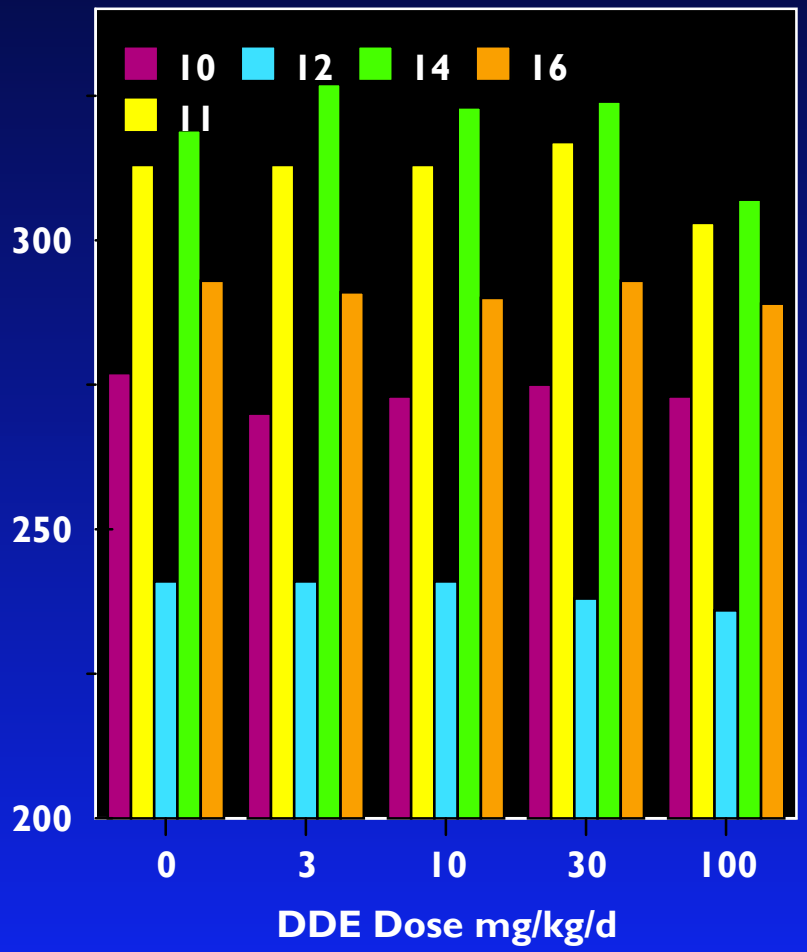


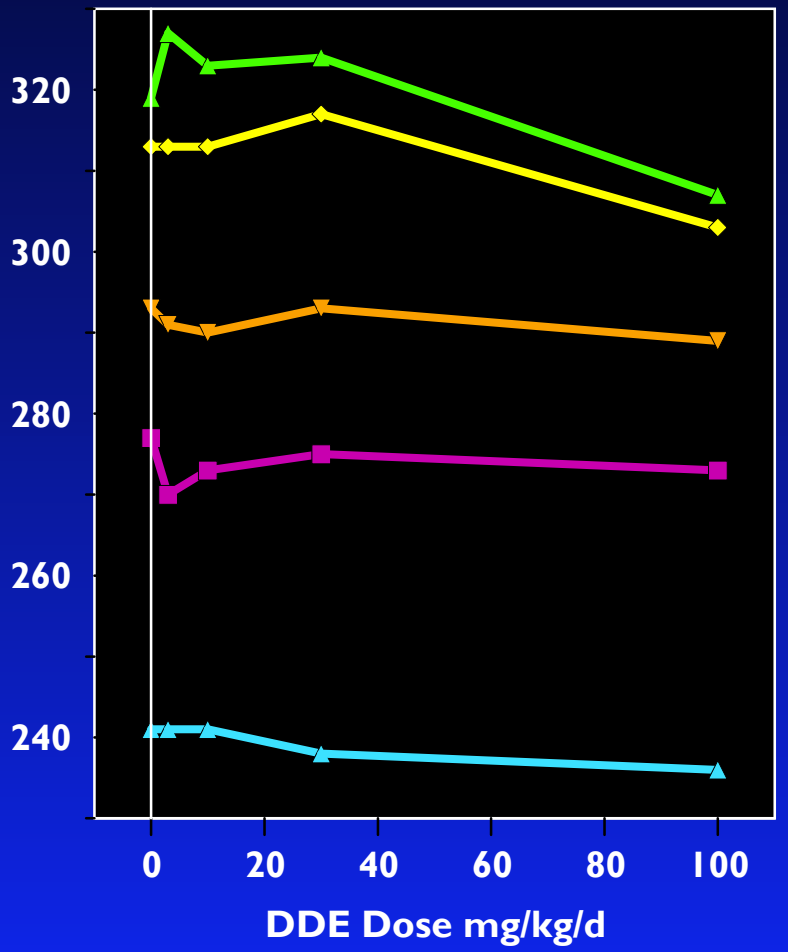
106a. Effect of p,p' DDE on Body weight at necropy. Data from five labs



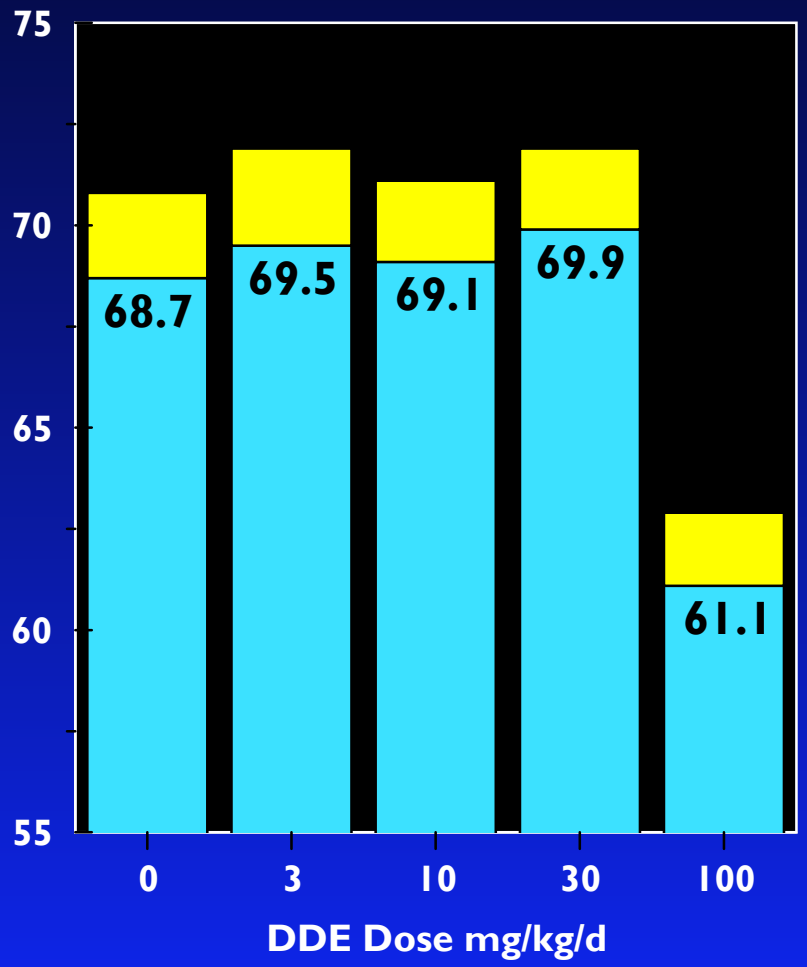


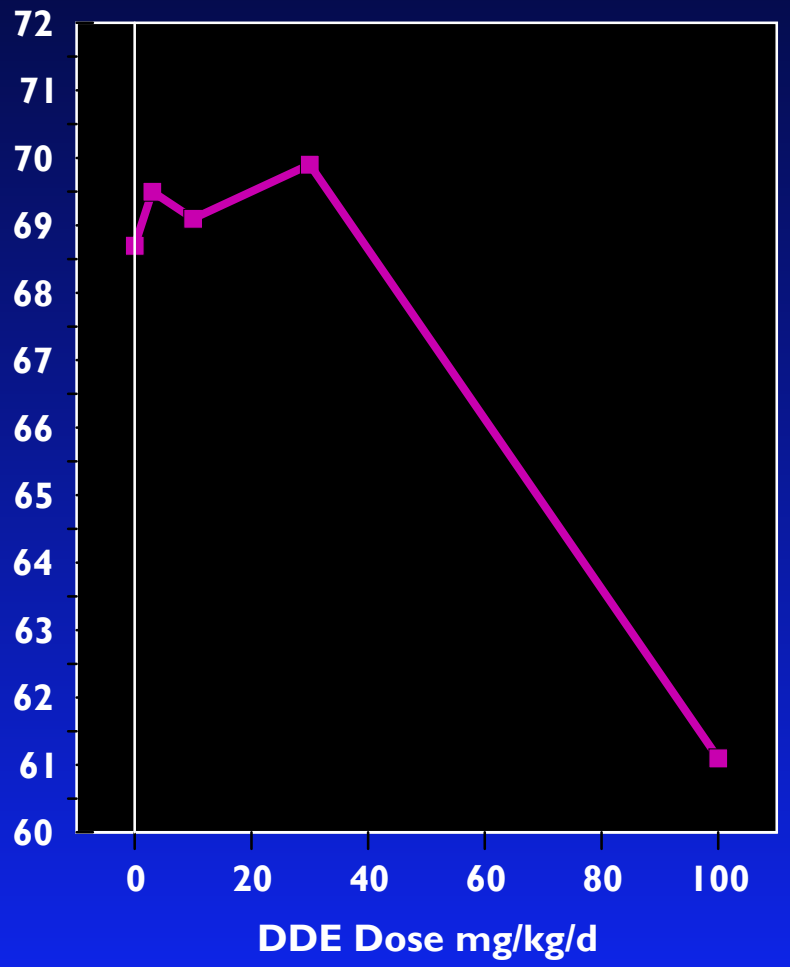
106b. Effect of p,p' DDE on Body weight at necropy. Data from five labs



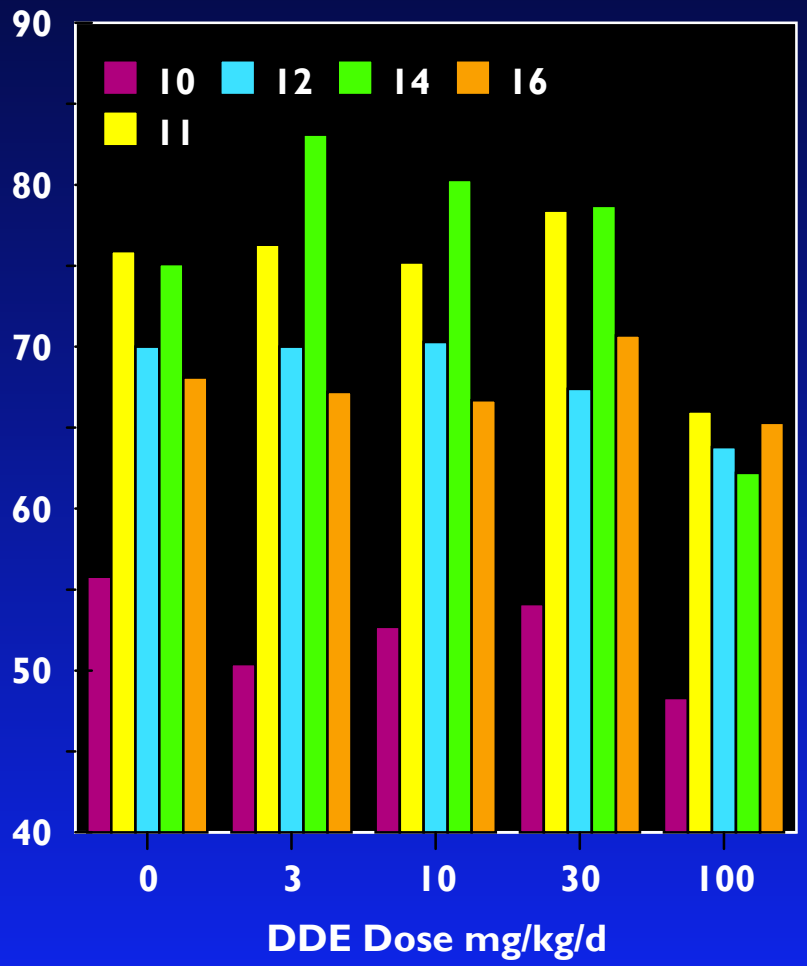


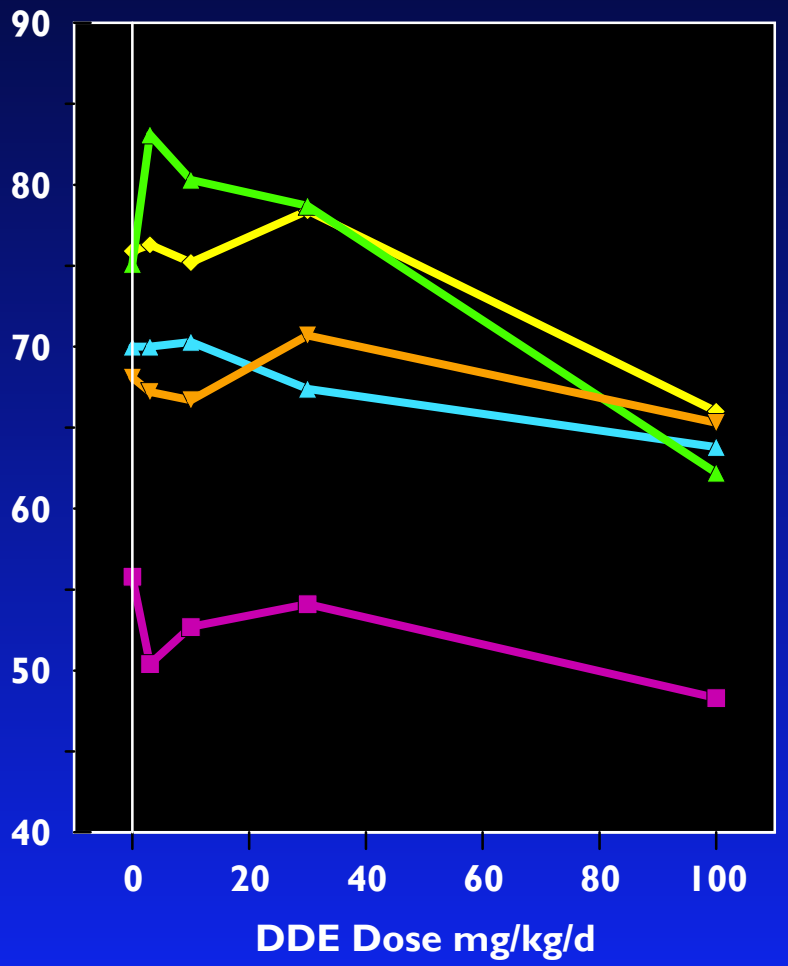
106c. Effect of p,p' DDE on Body weight gain during dosing to necropy. Data from five labs





106d. Effect of p,p' DDE on Body weight gain through dosing to necropy. Data from five labs

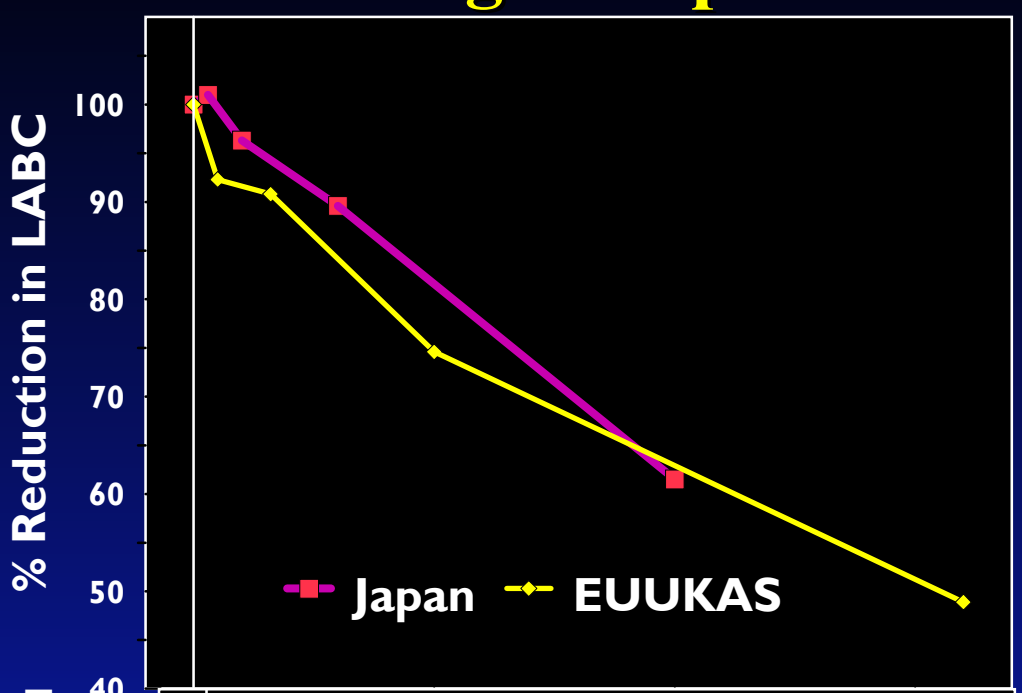


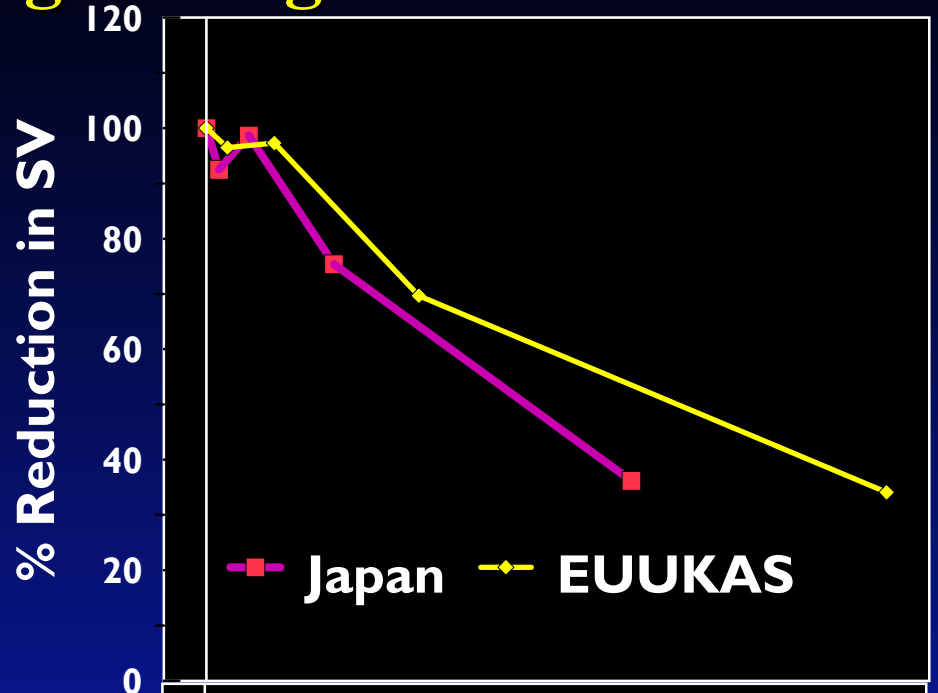


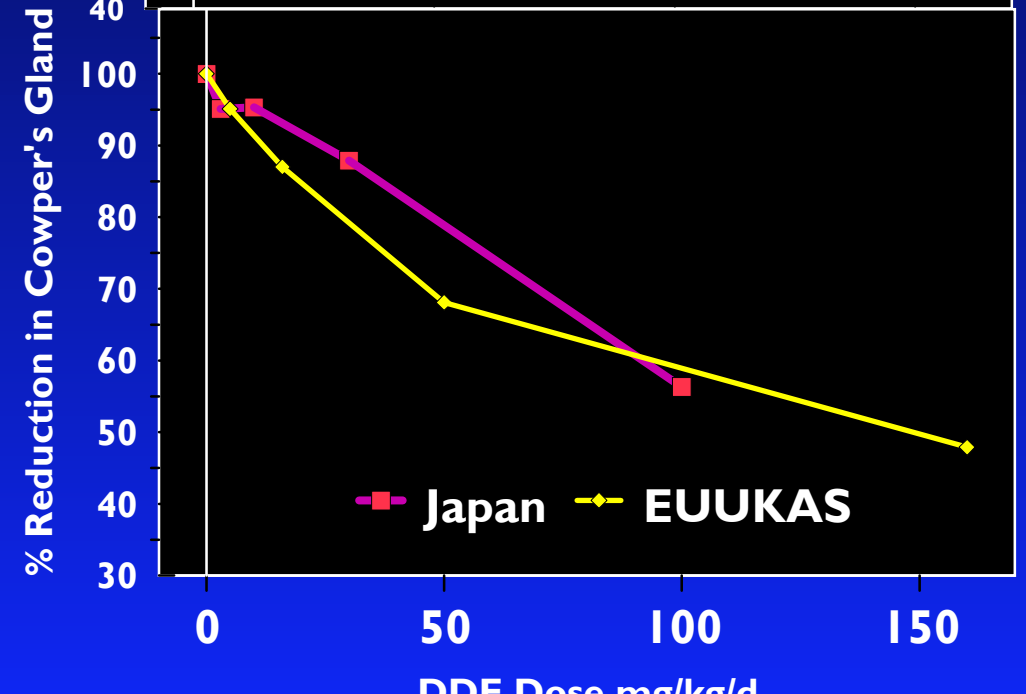
Oral p,p DDE antagonizes the effects of TP sc at 0.2 and 0.4 mg/kg/d for ten days in the Hershberger assay

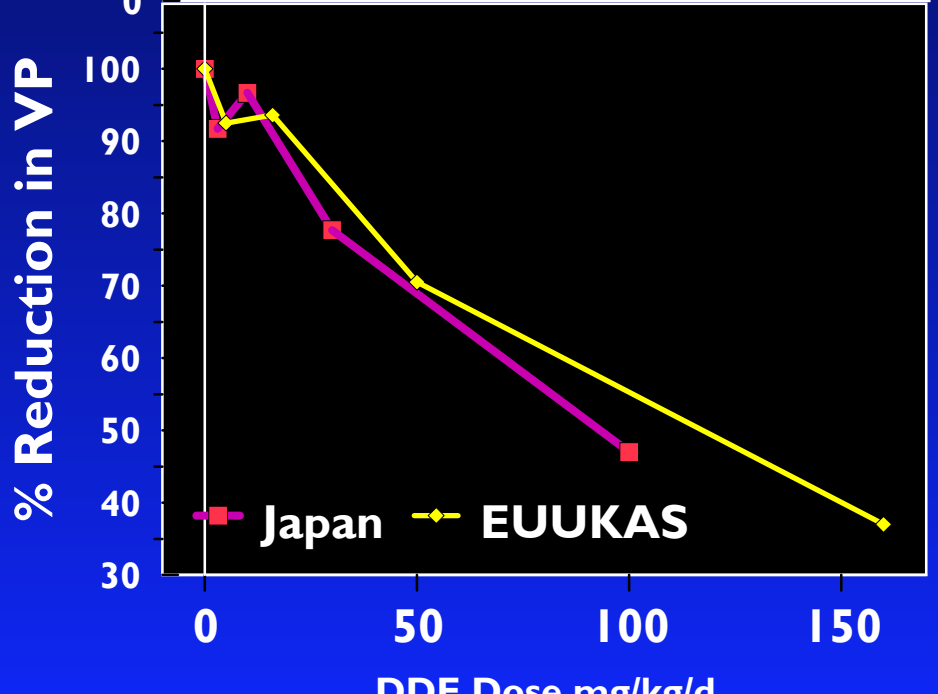
EUUKAS AND JAPANESE DATA

107. Effects of p,p DDE from two protocols/groups on androgen-dependent organ weights

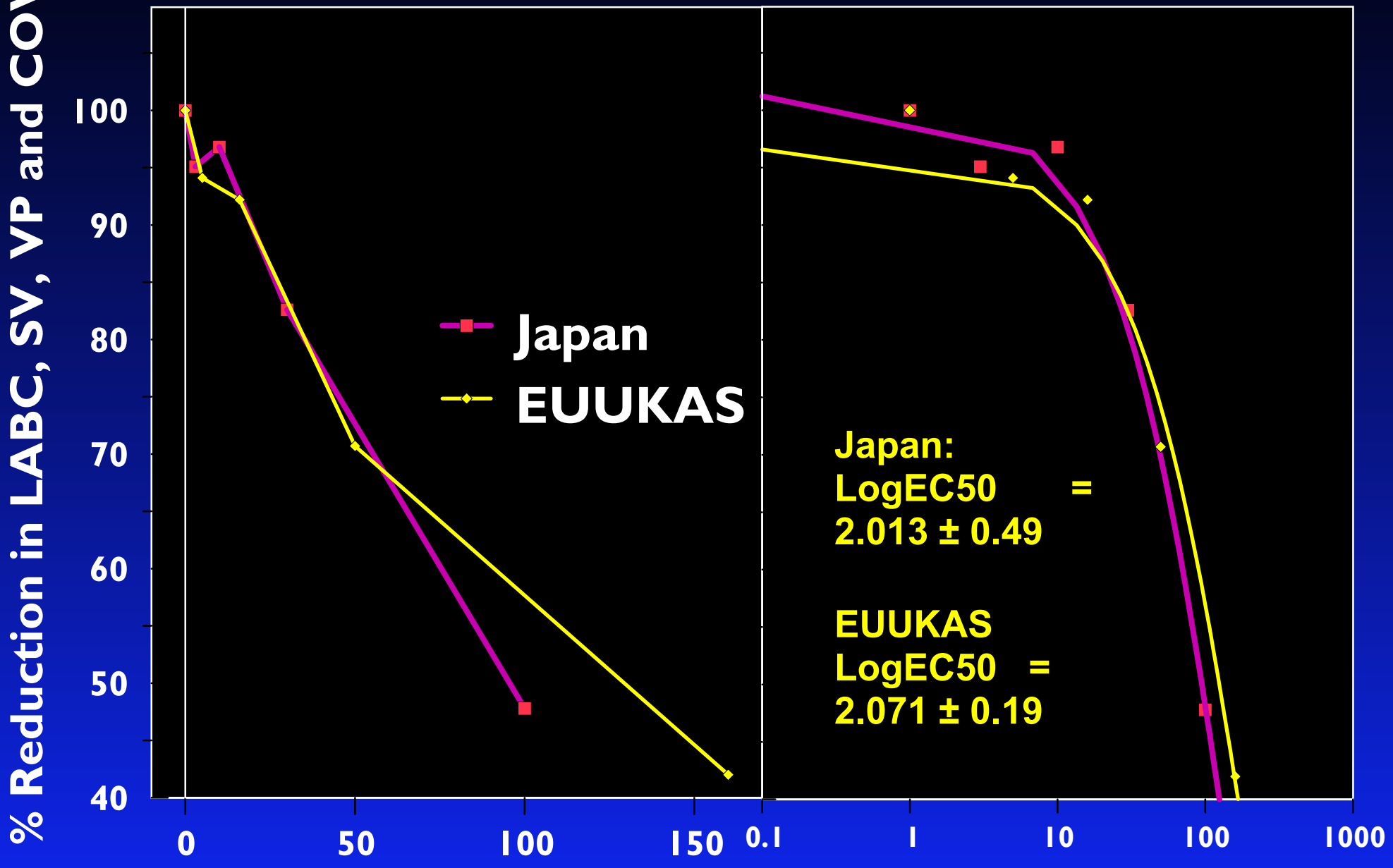








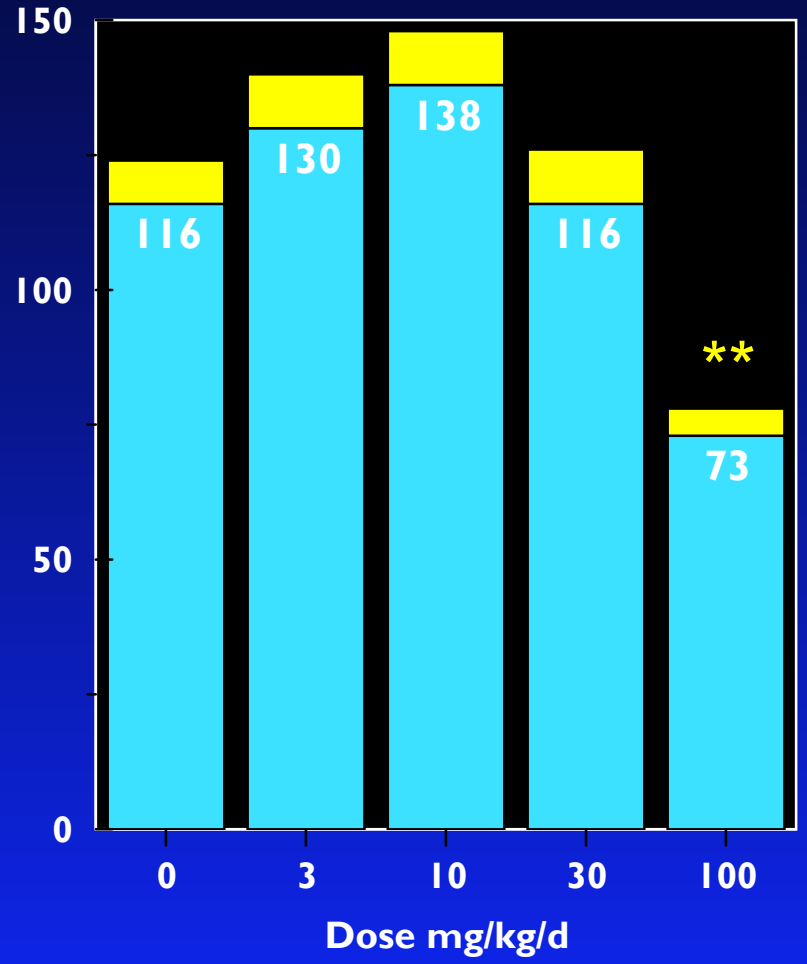
108. Effects of p,p DDE from two groups on androgen-dependent organ weights

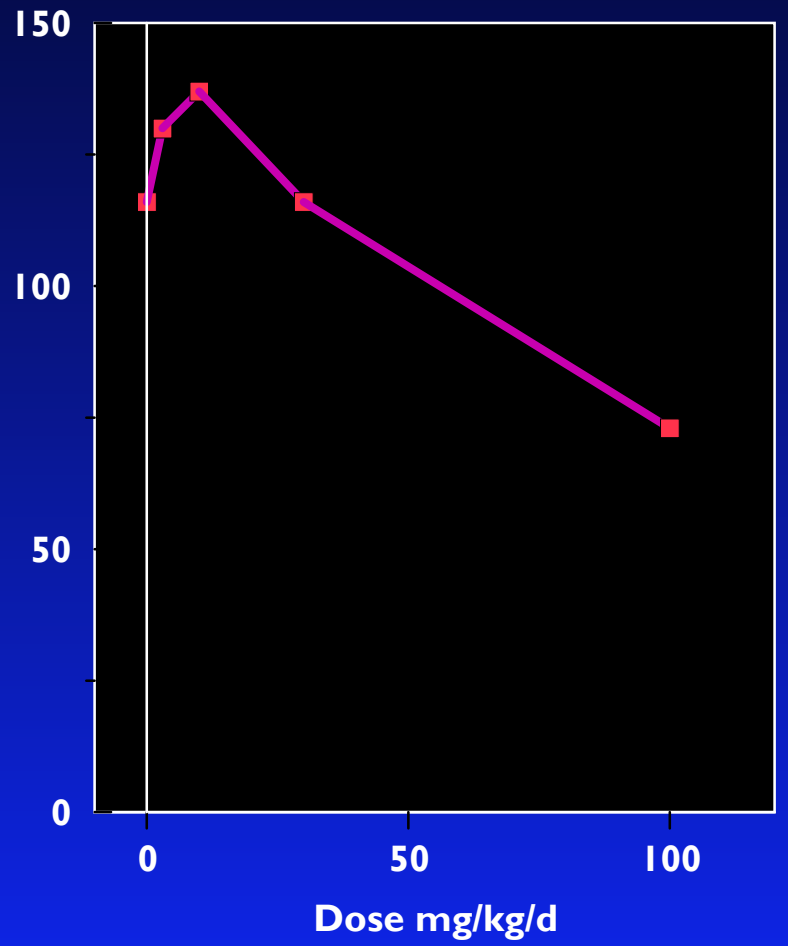


Phase 2
OECD Hershberger Assay
Interlaboratory study

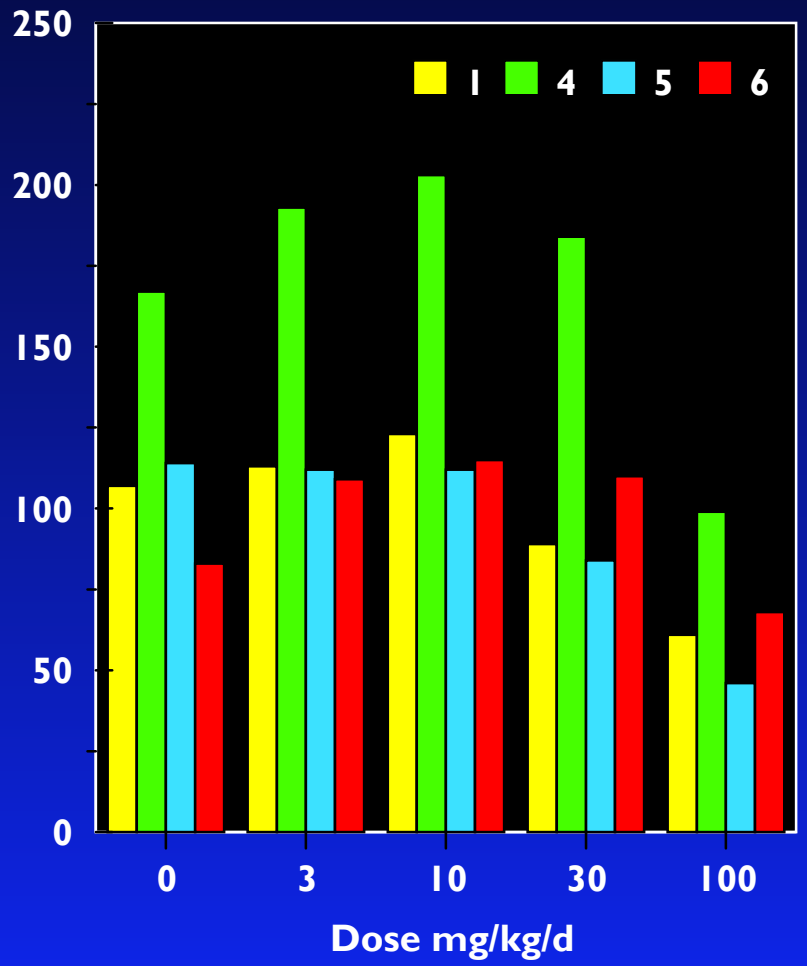
Linuron data EUUKAS

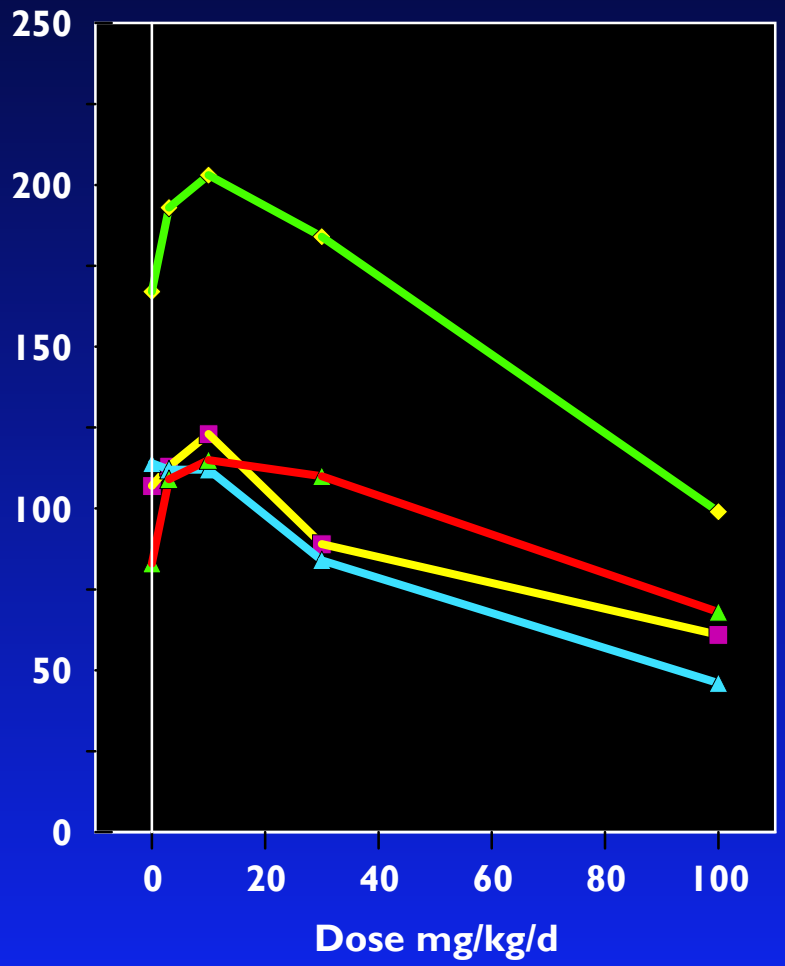
109. Effect of Linuron on Ventral Prostate weights. Data from four labs



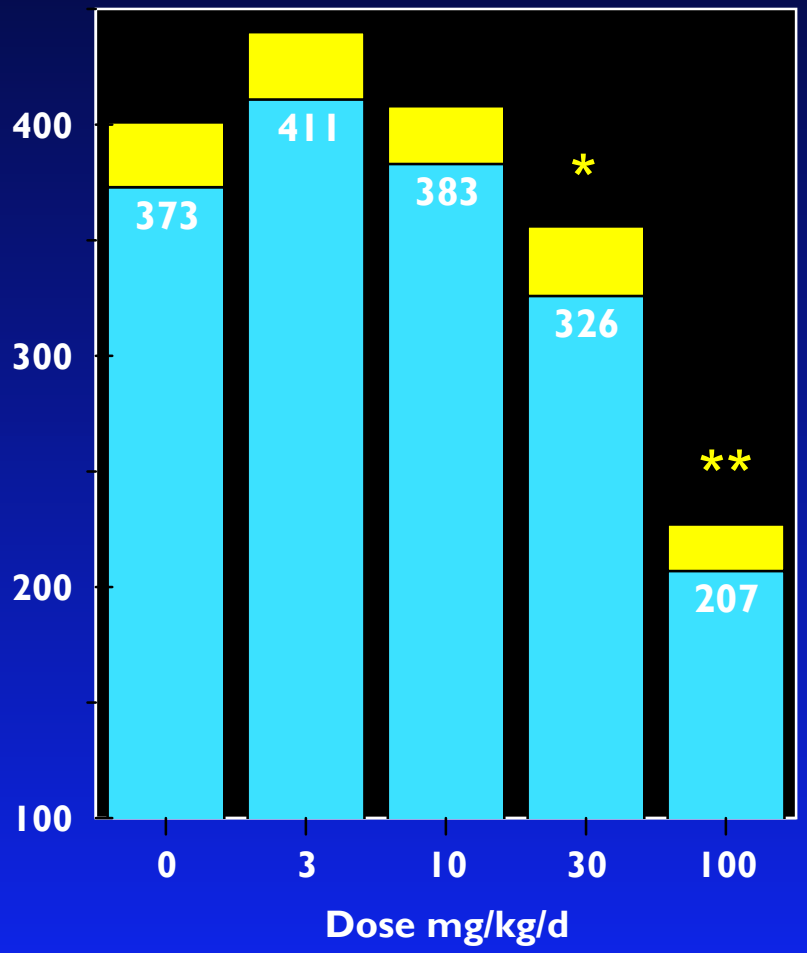


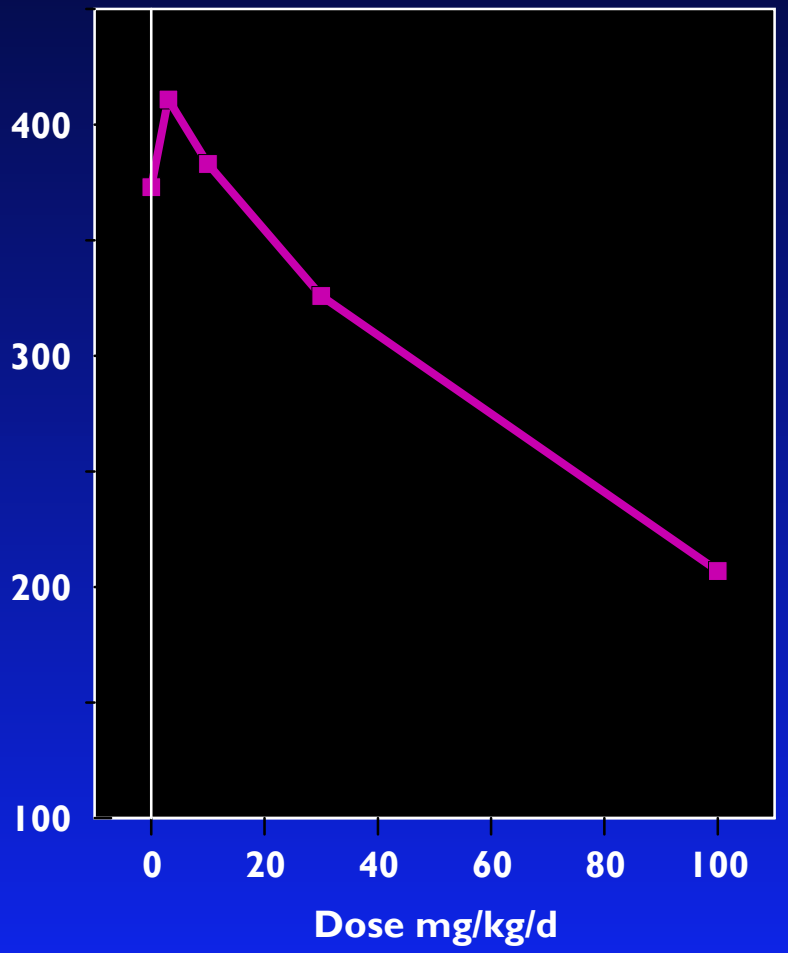
110. Effect of Linuron on VP weights. Data from four labs



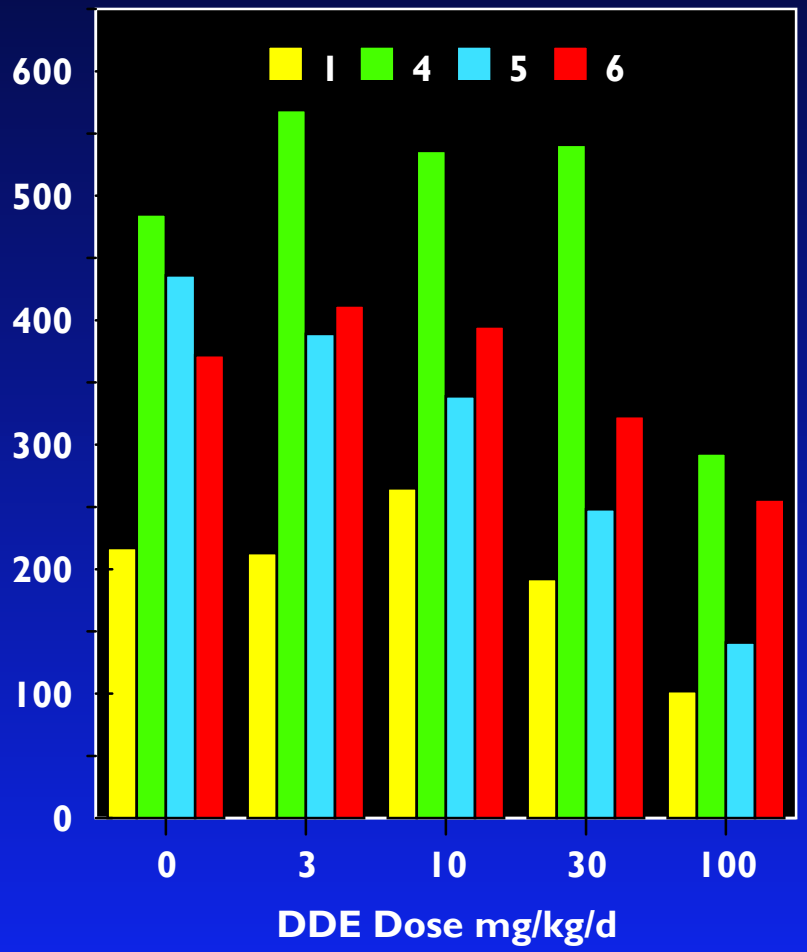


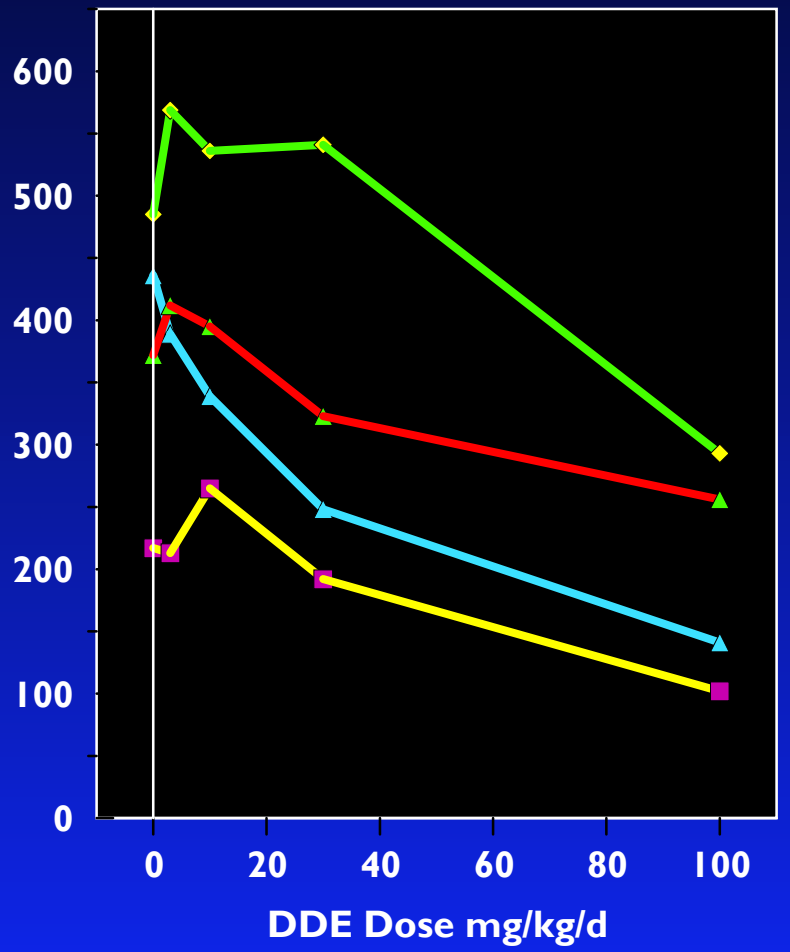
111. Effect of Linuron on Seminal Vesicle weights. Data from four labs



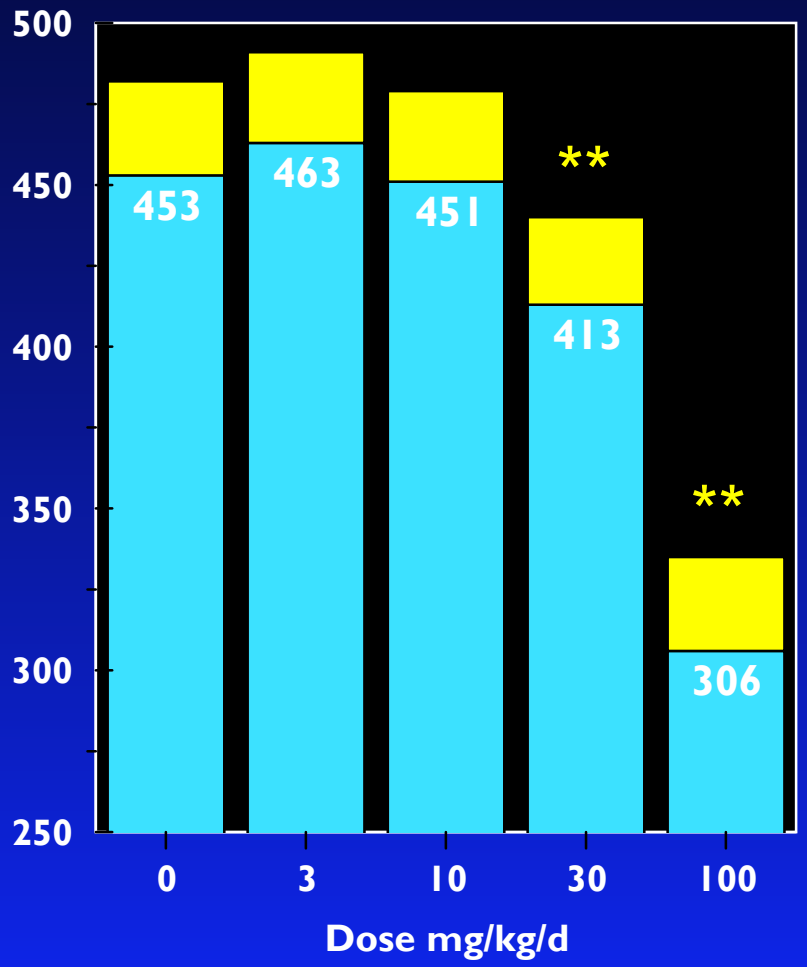


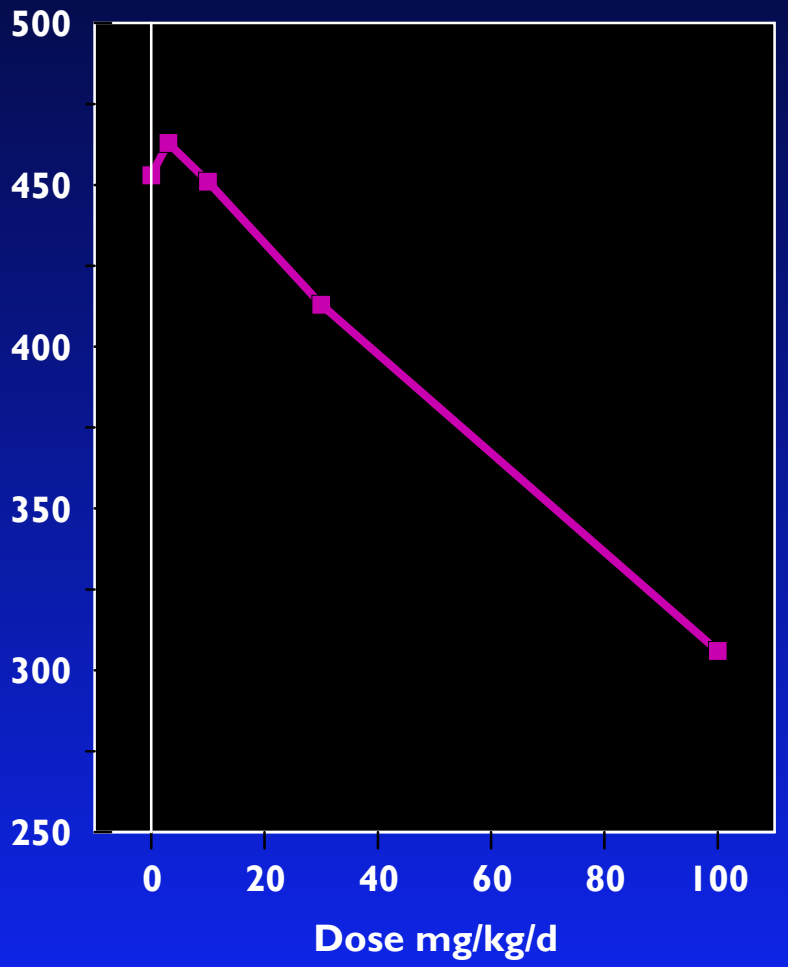
112. Effect of Linuron on Seminal Vesicle weights. Data from four labs



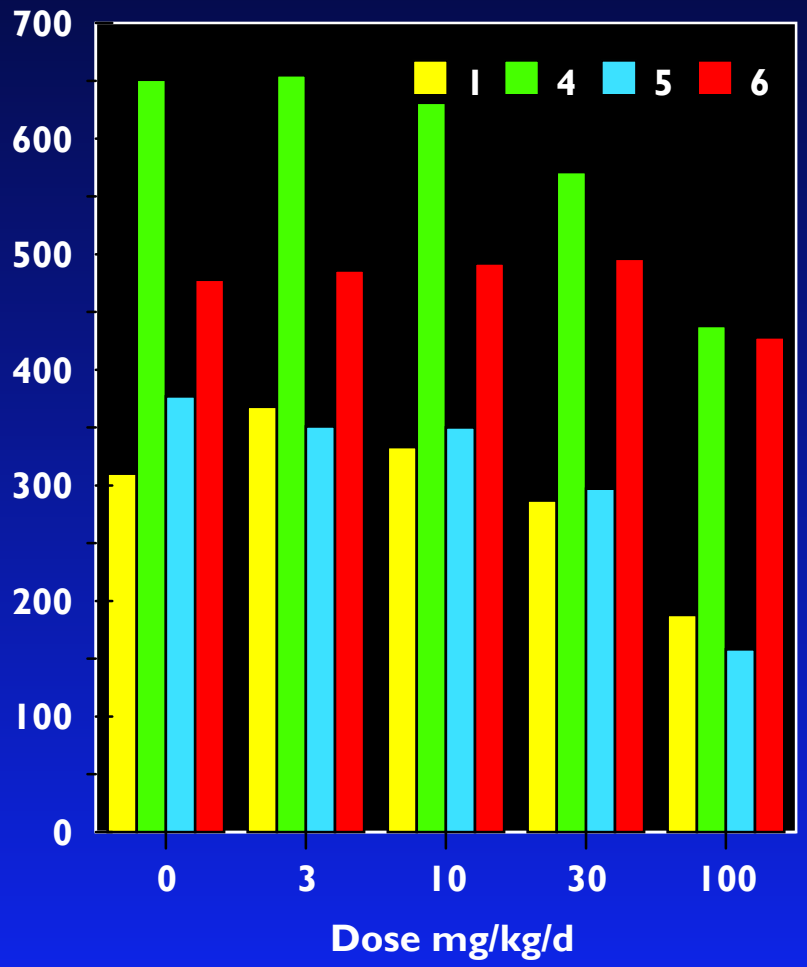


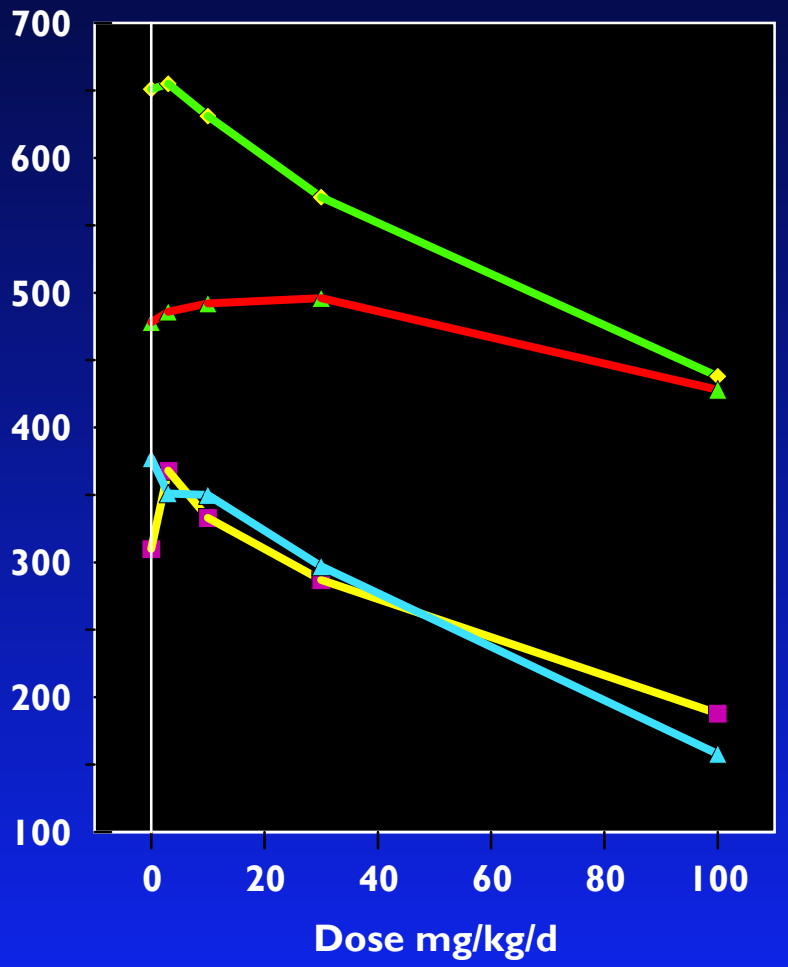
113. Effect of Linuron on LABC weights. Data from four labs



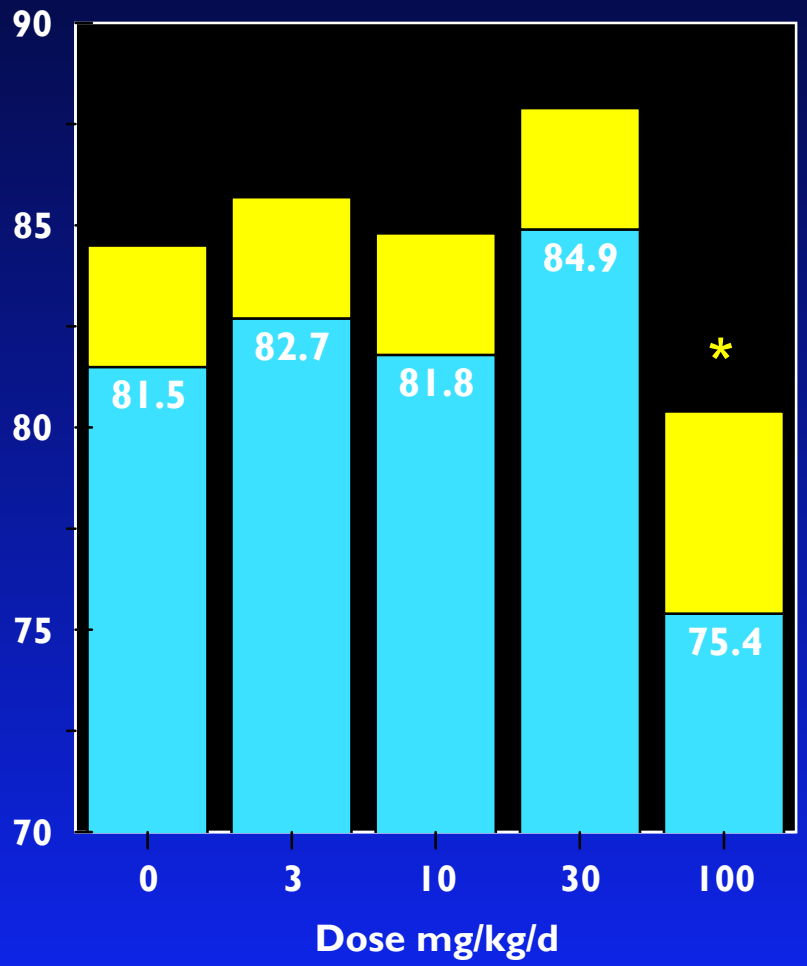


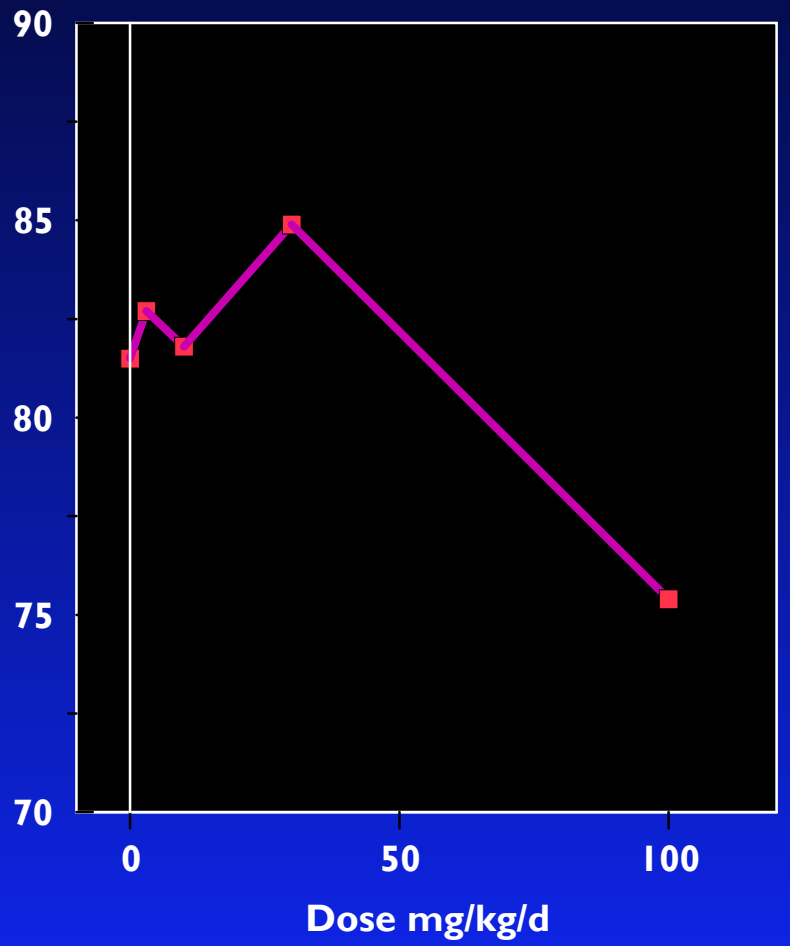
114. Effect of Linuron on LABC weights. Data from four labs



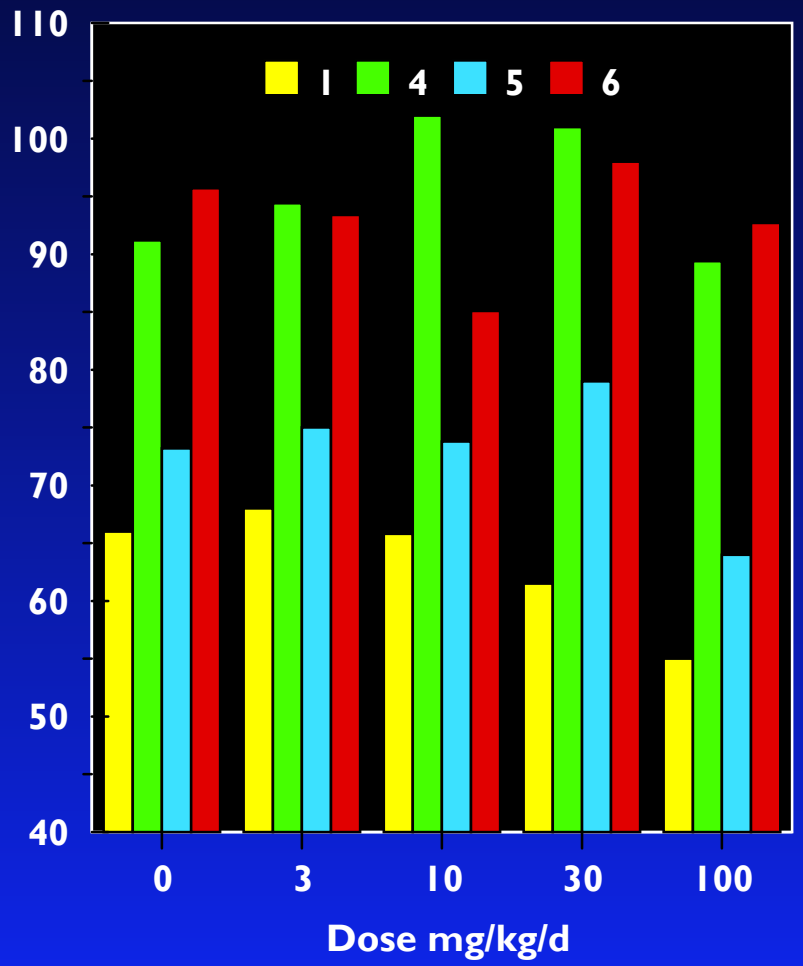


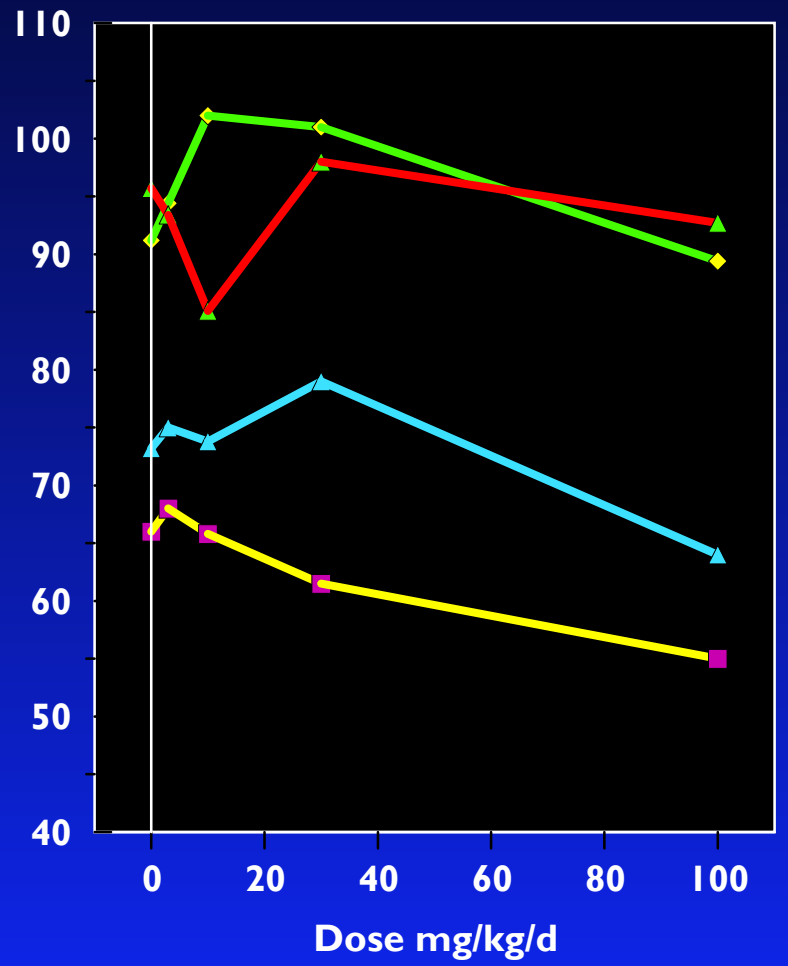
115. Effect of Linuron on Glans penis weights. Data from four labs



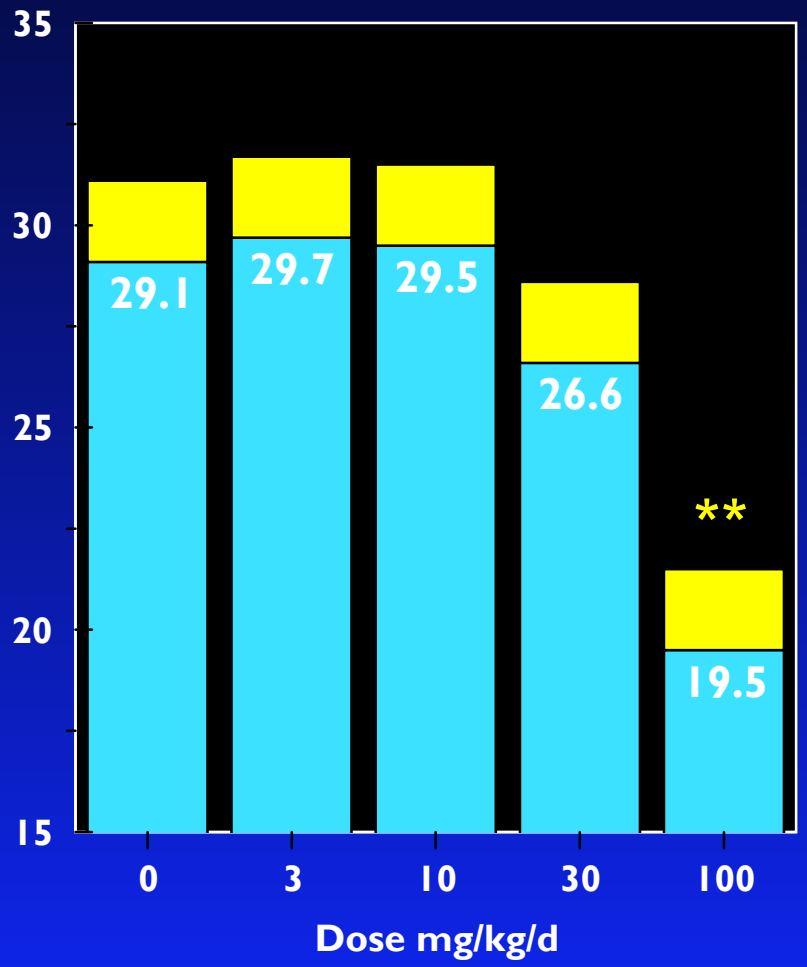


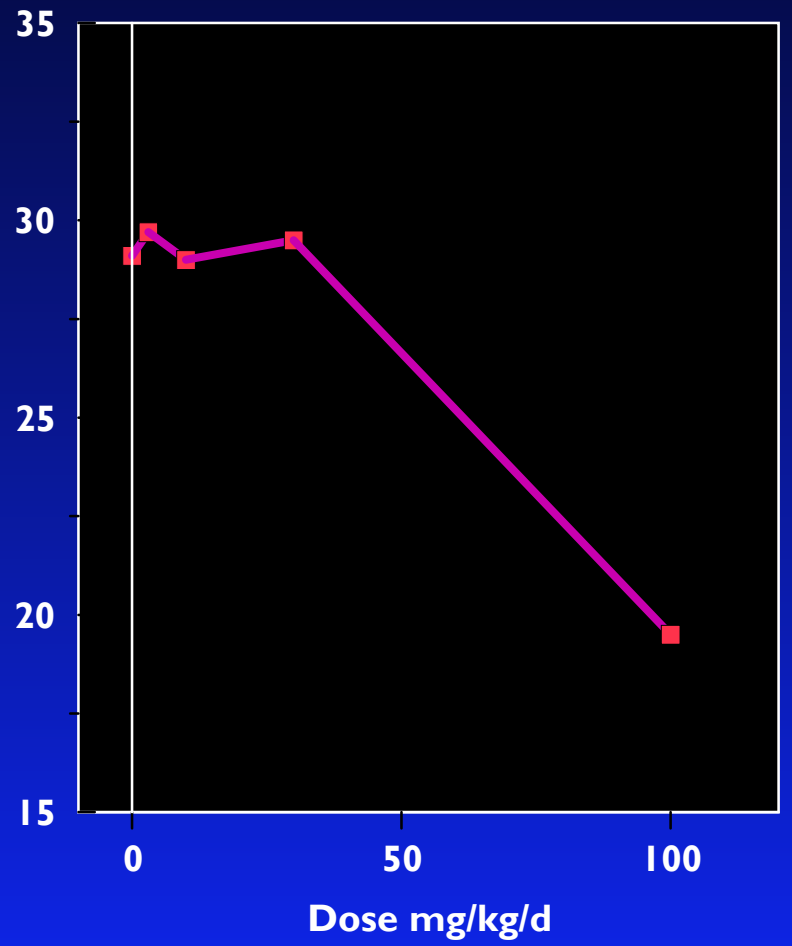
116. Effect of Linuron on Glans Penis weights. Data from four labs



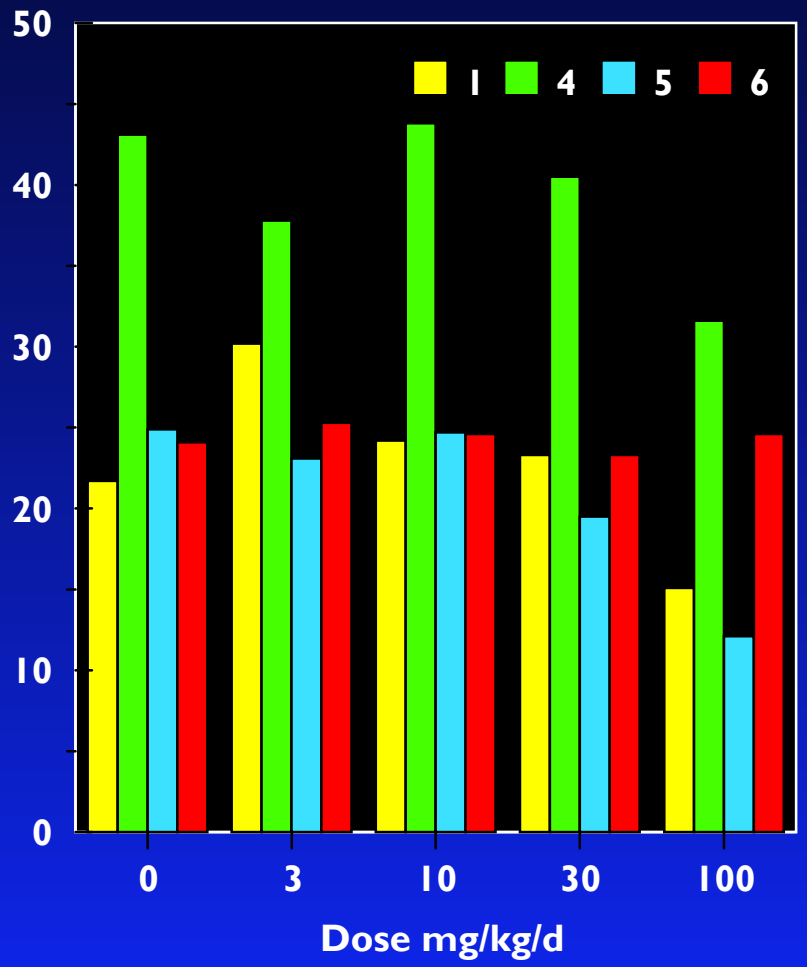


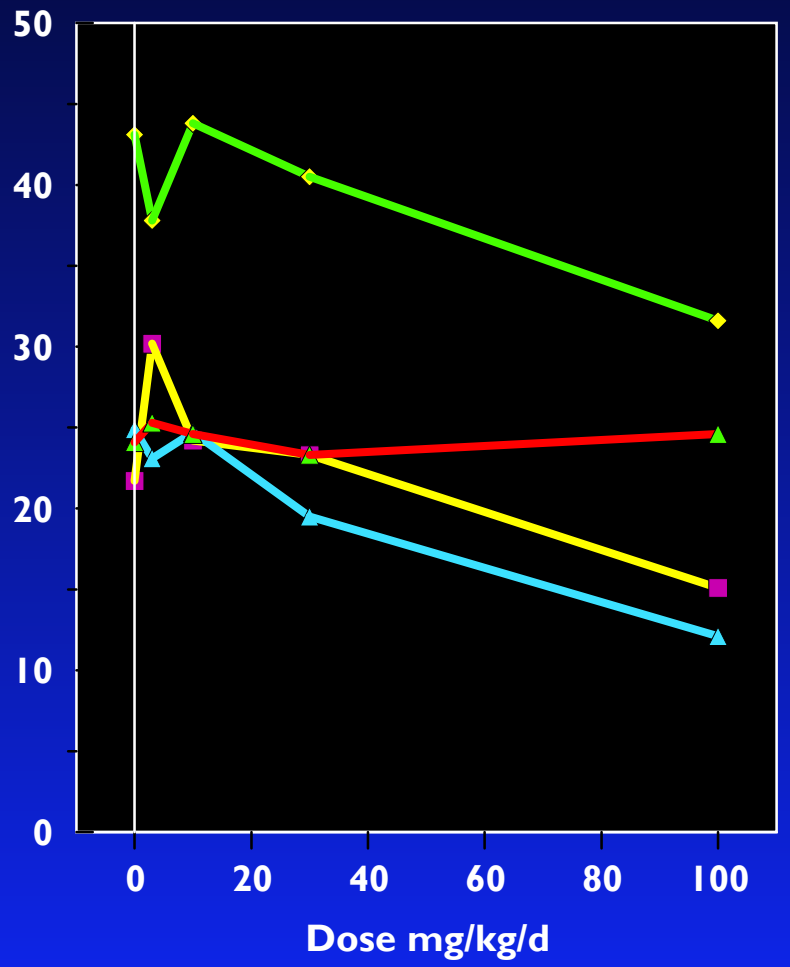
117. Effect of Linuron on Cowper's gland weights. Data from four labs



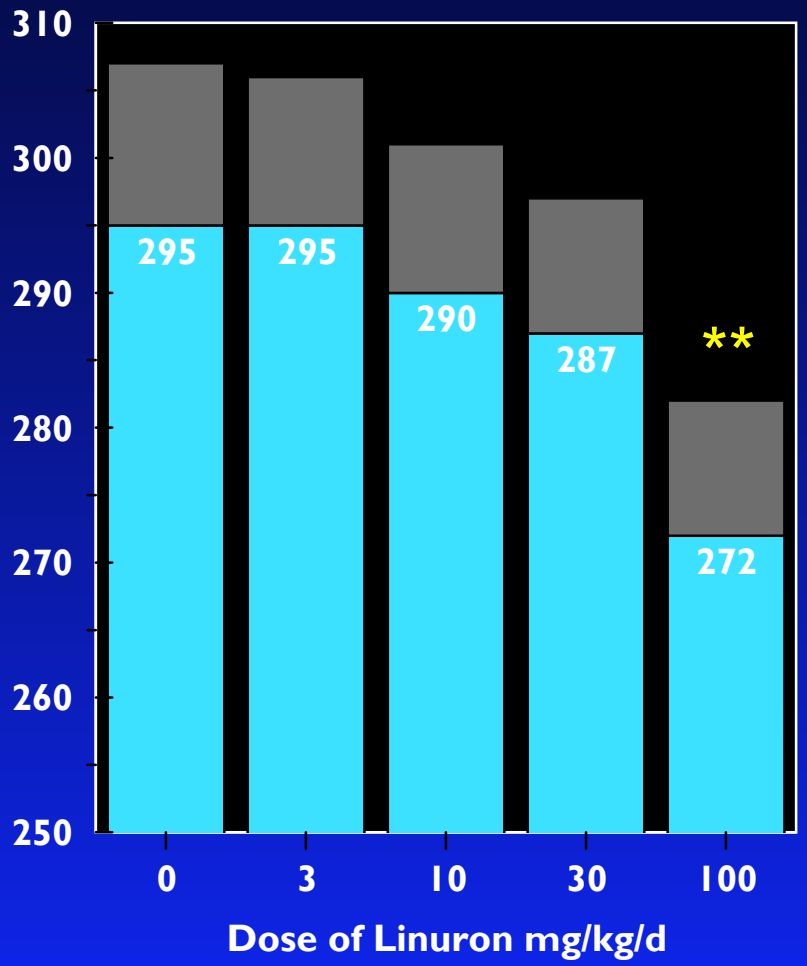


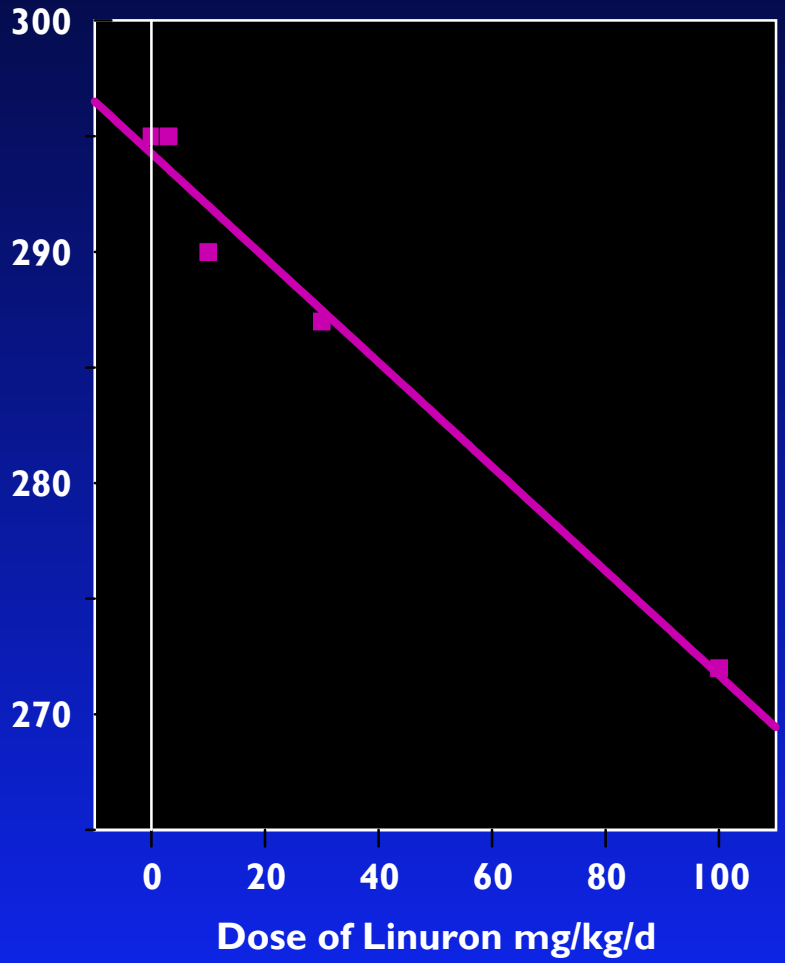
118. Effect of Linuron on Cowper's gland weights. Data from four labs



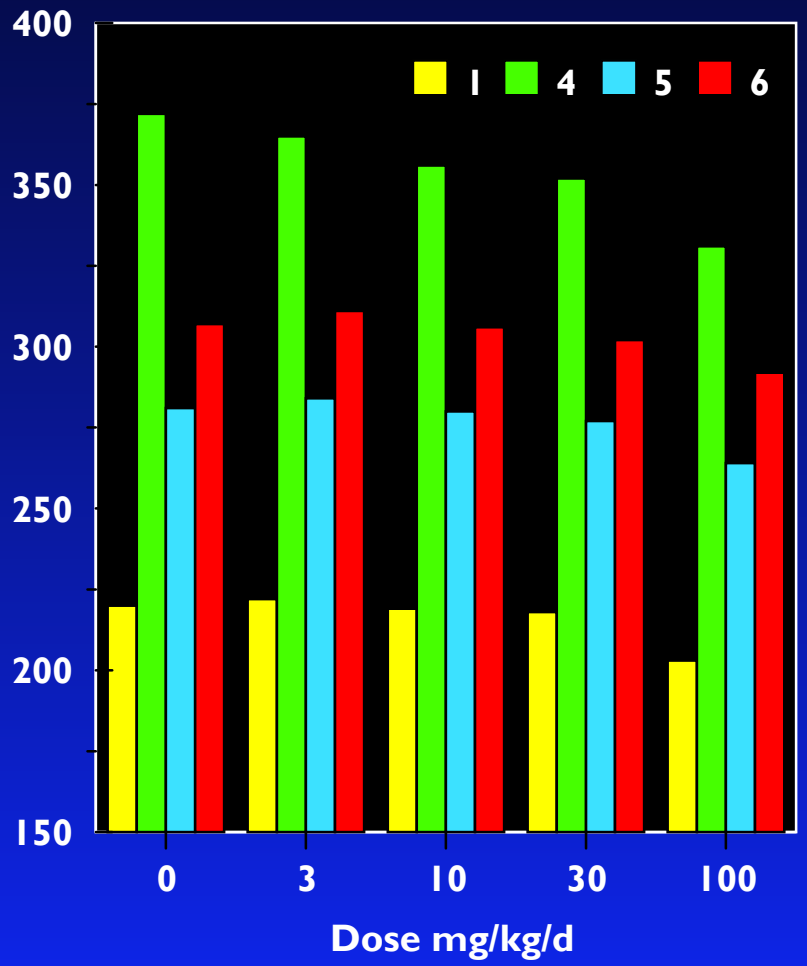


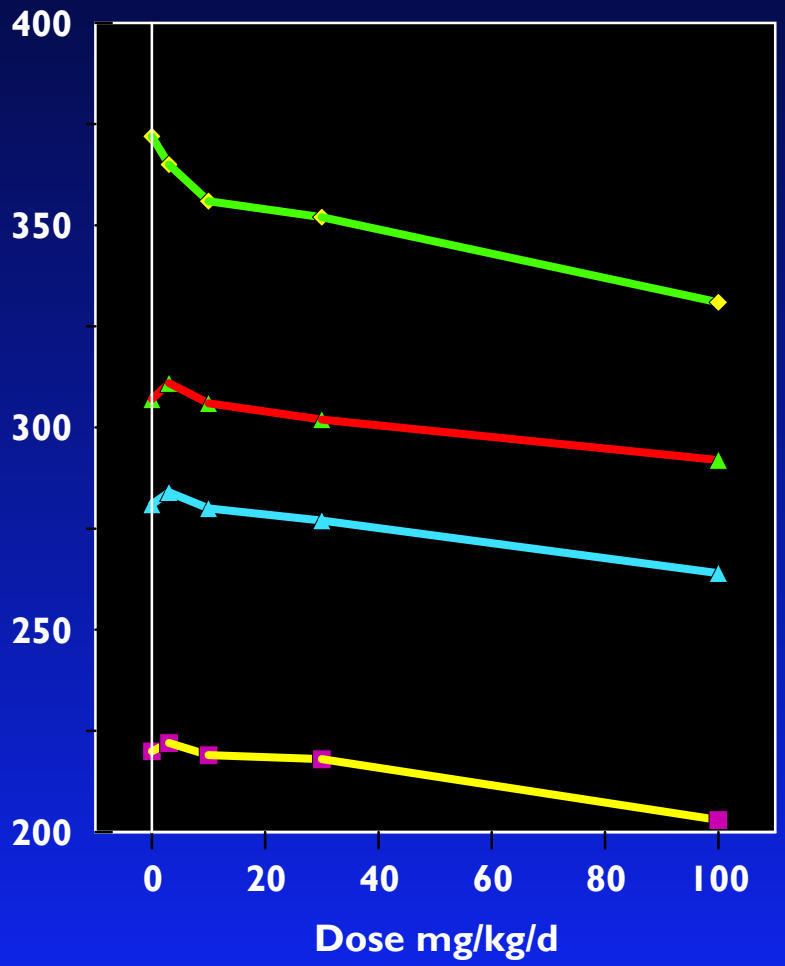
119. Effects of Linuron on Body weight at necropsy





119b. Effect of Linuron on Body weights. Data from four labs

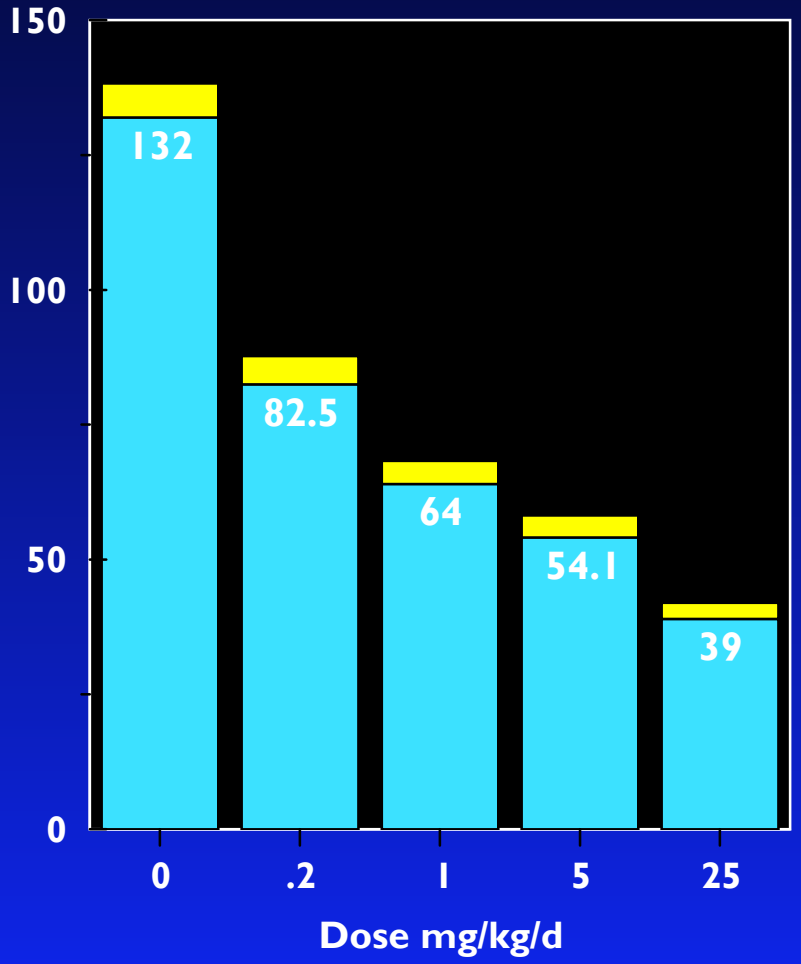


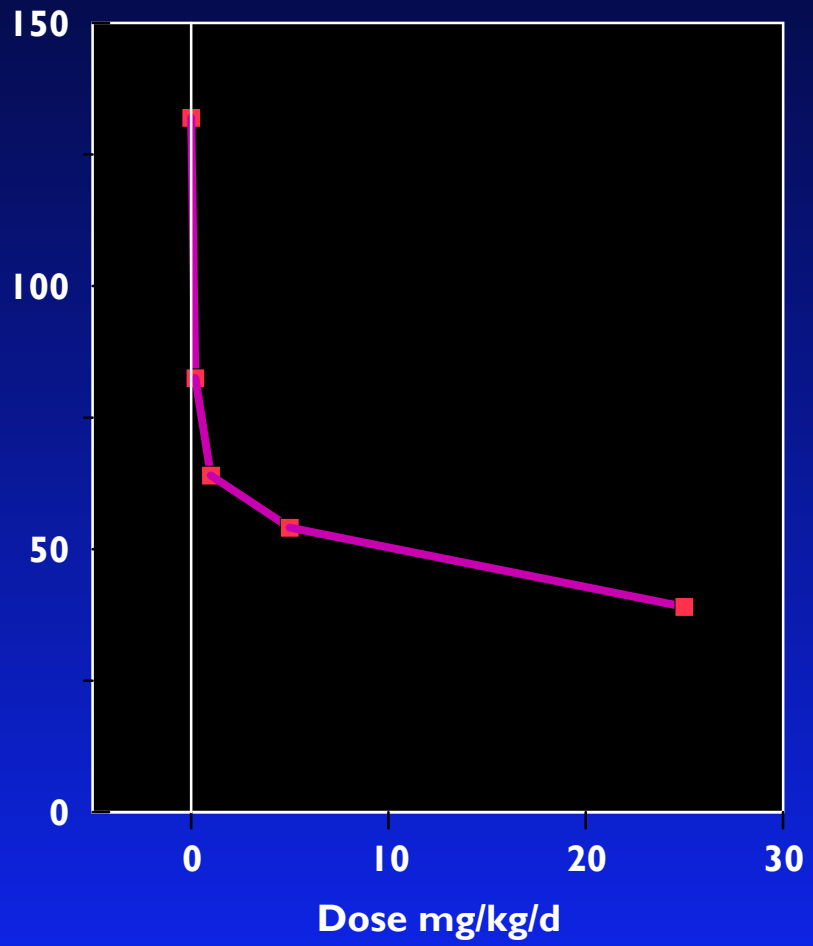


Phase 2
OECD Hershberger Assay
Interlaboratory study

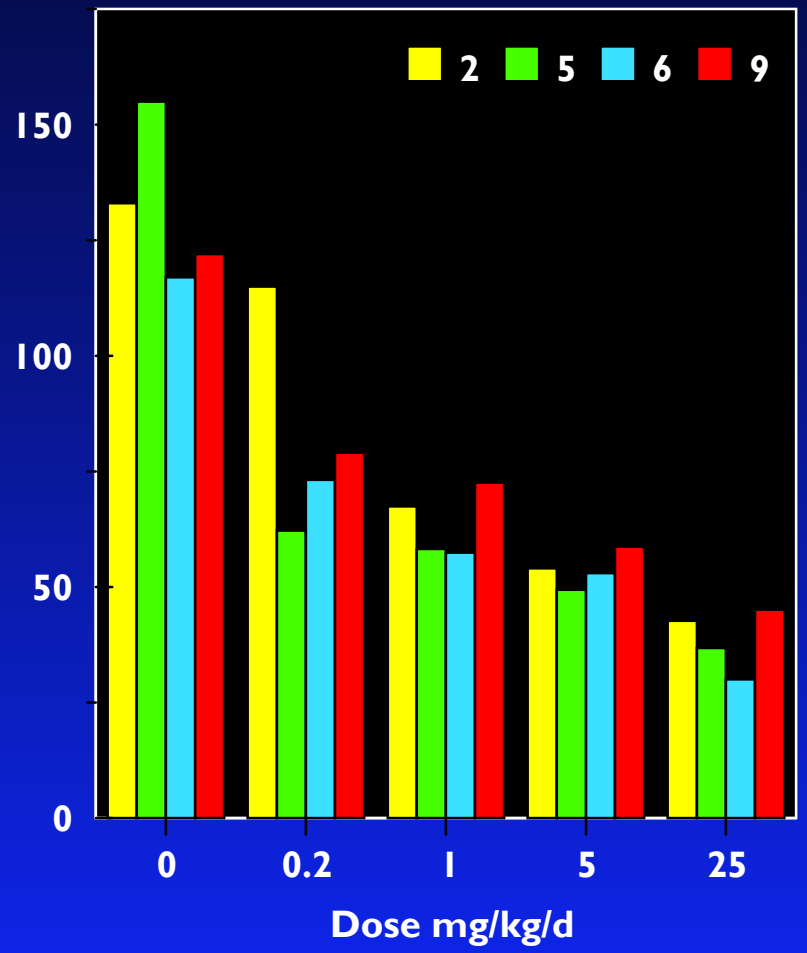
Finasteride data EUUKAS

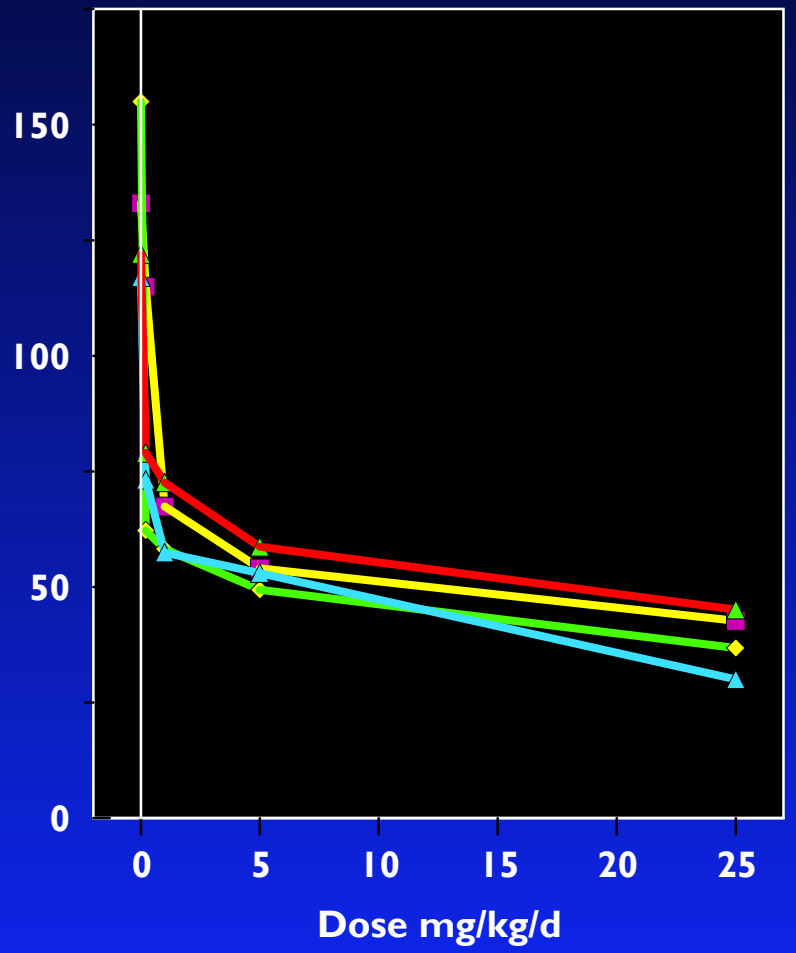
120. Effect of Finasteride on Ventral Prostate weights. All values differ from control (p<0.01). Data from four labs



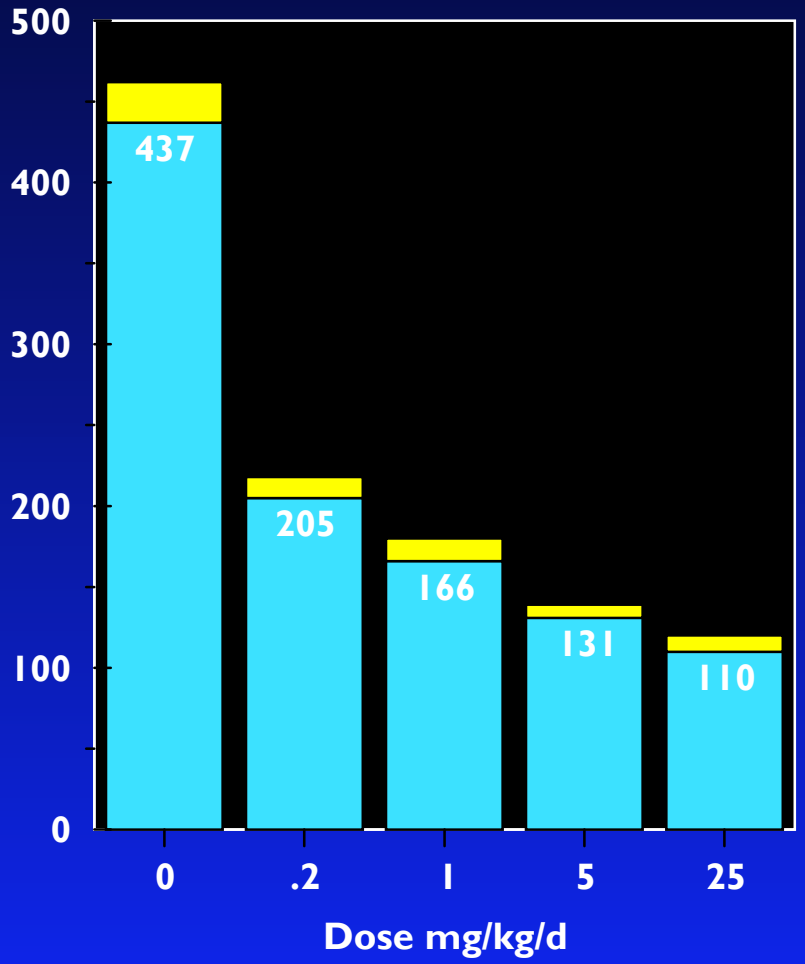


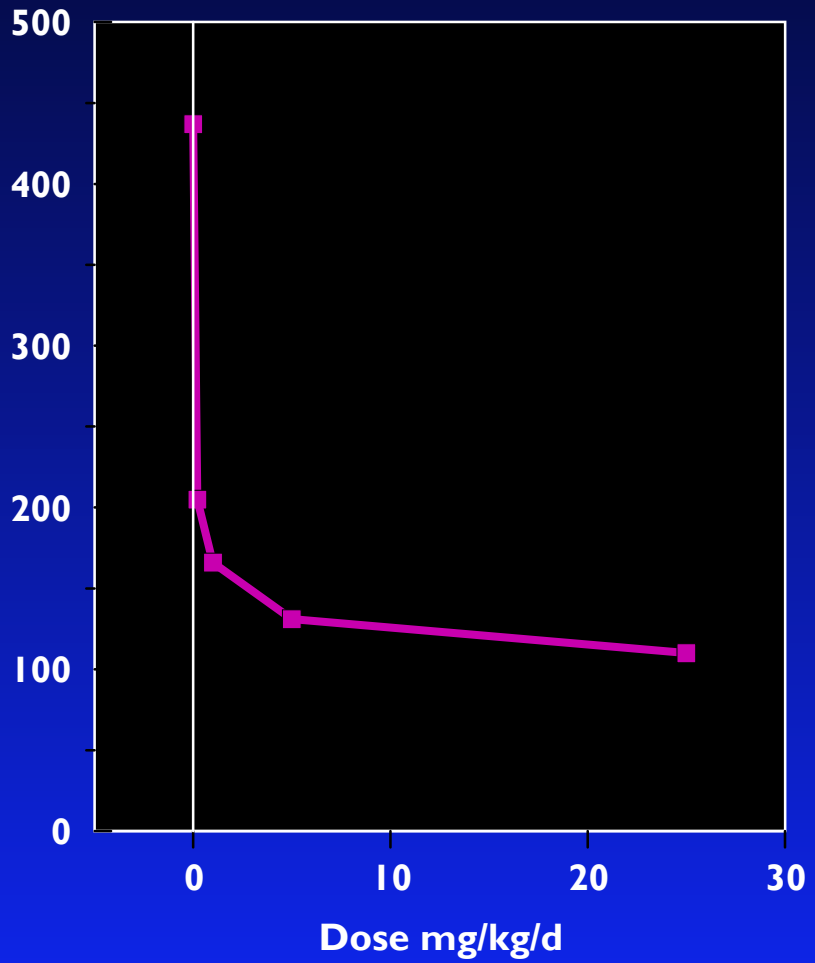
121. Effect of Finasteride on VP weights. Data from four labs



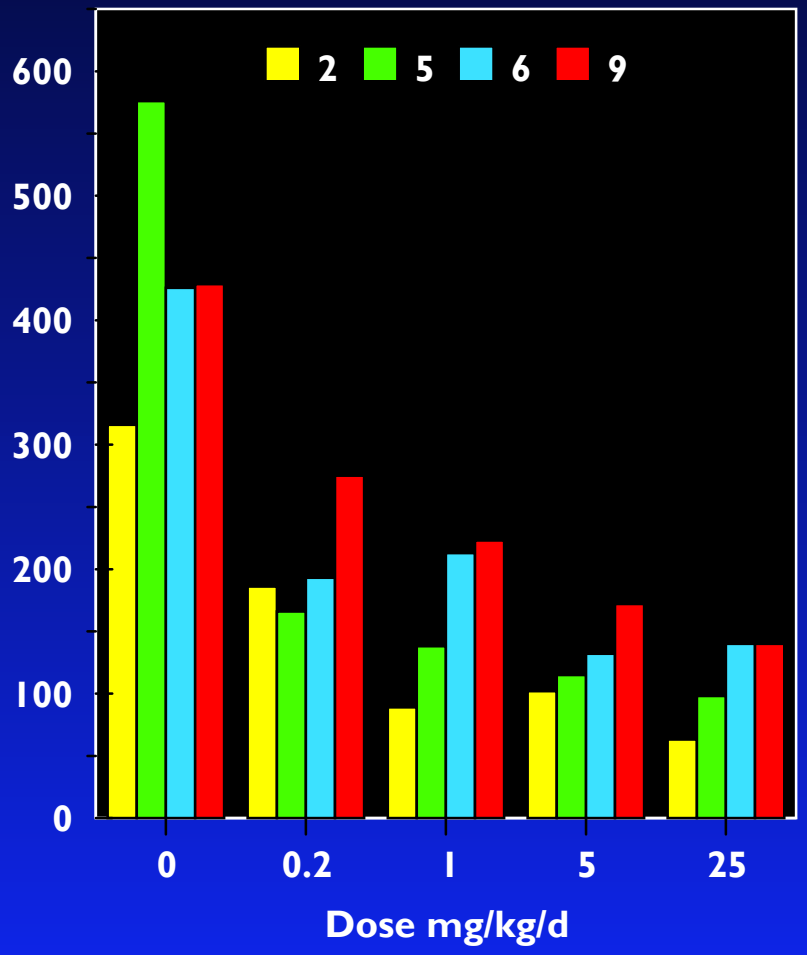


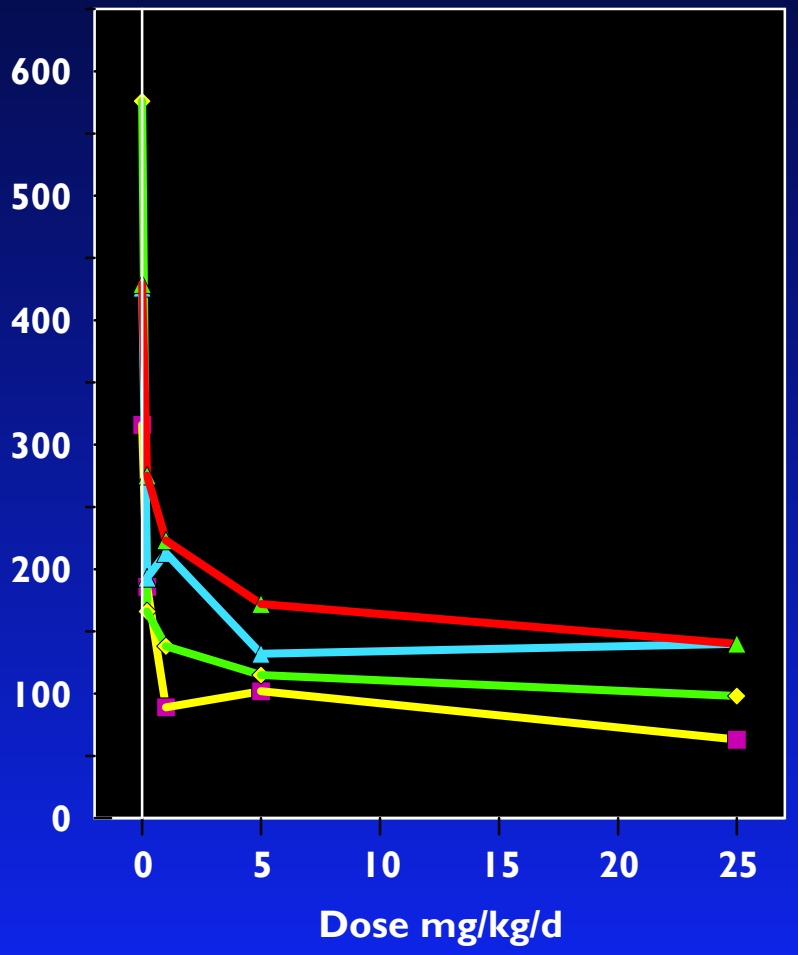
122. Effect of Finasteride on Seminal Vesicle weights. All values differ from control (p<0.01). Data from four labs



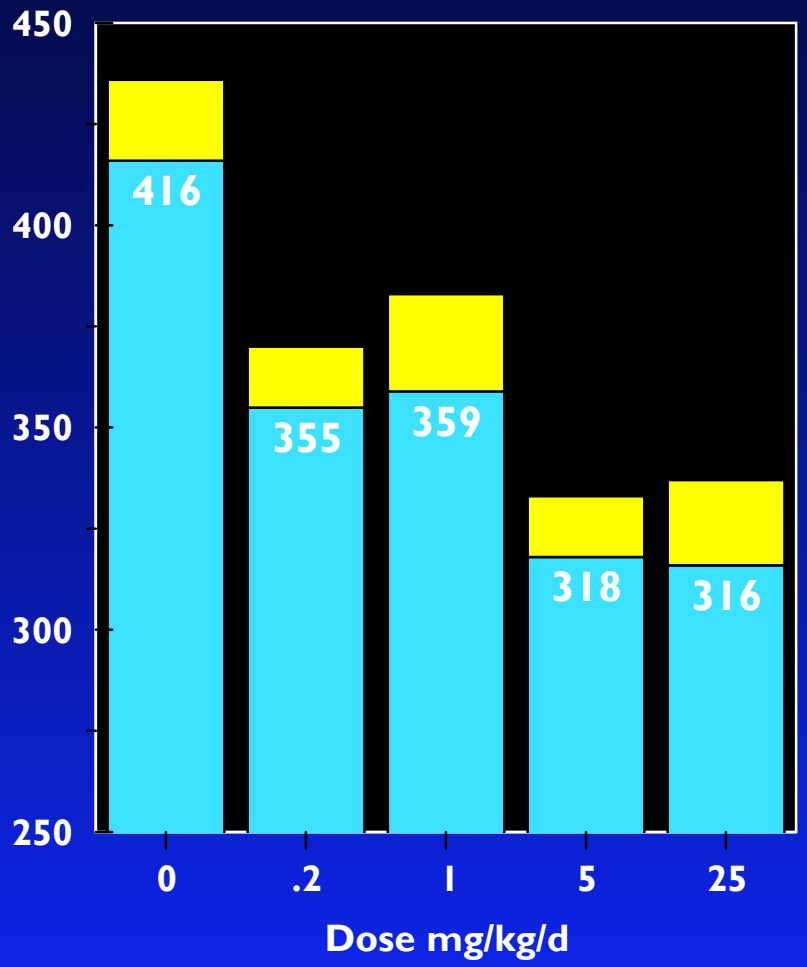


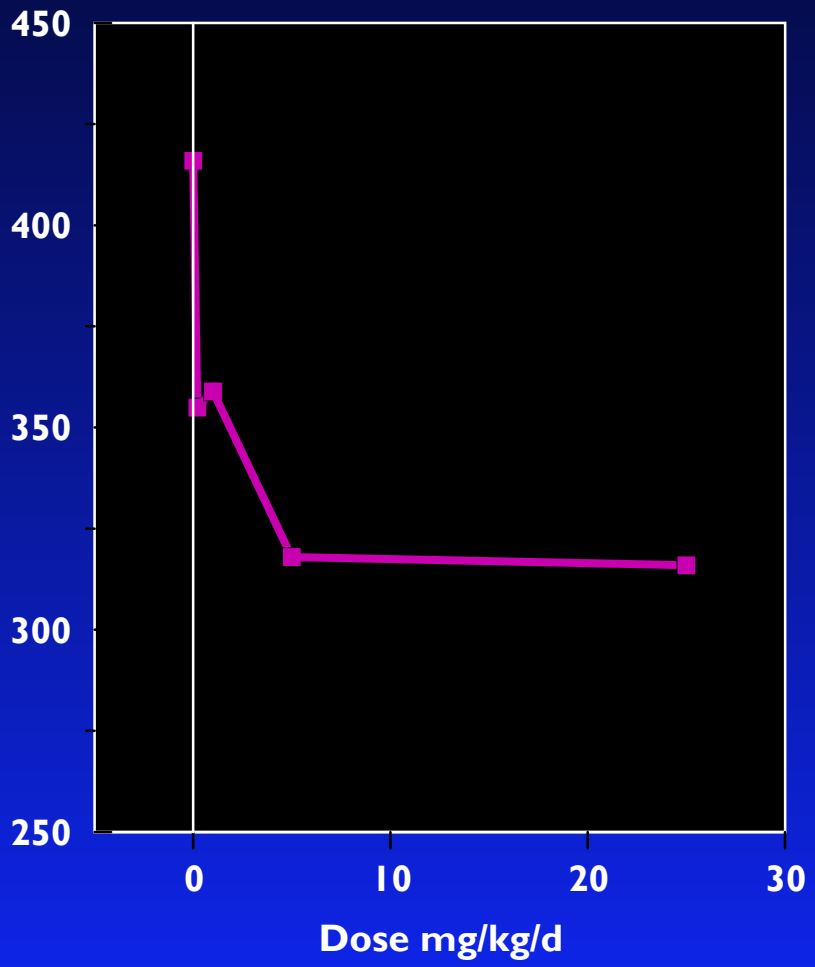
123. Effect of Finasteride on Seminal Vesicle weights. Data from four labs



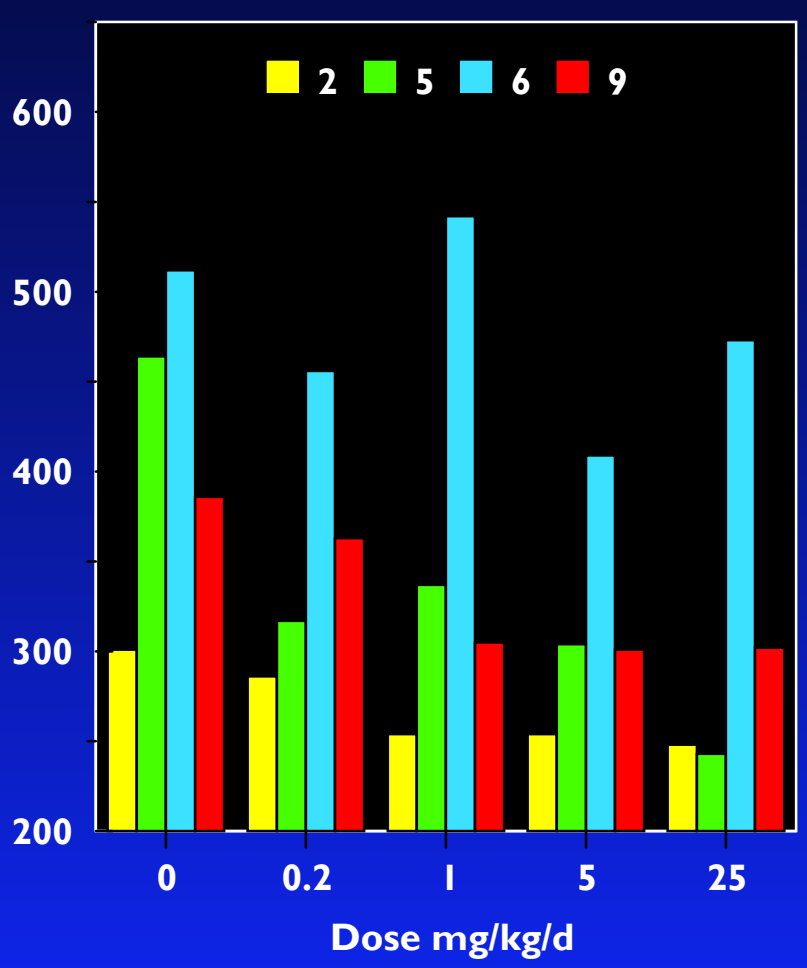


124. Effect of Finasteride on LABC weights. All values differ from control (p<0.01). Data from four labs

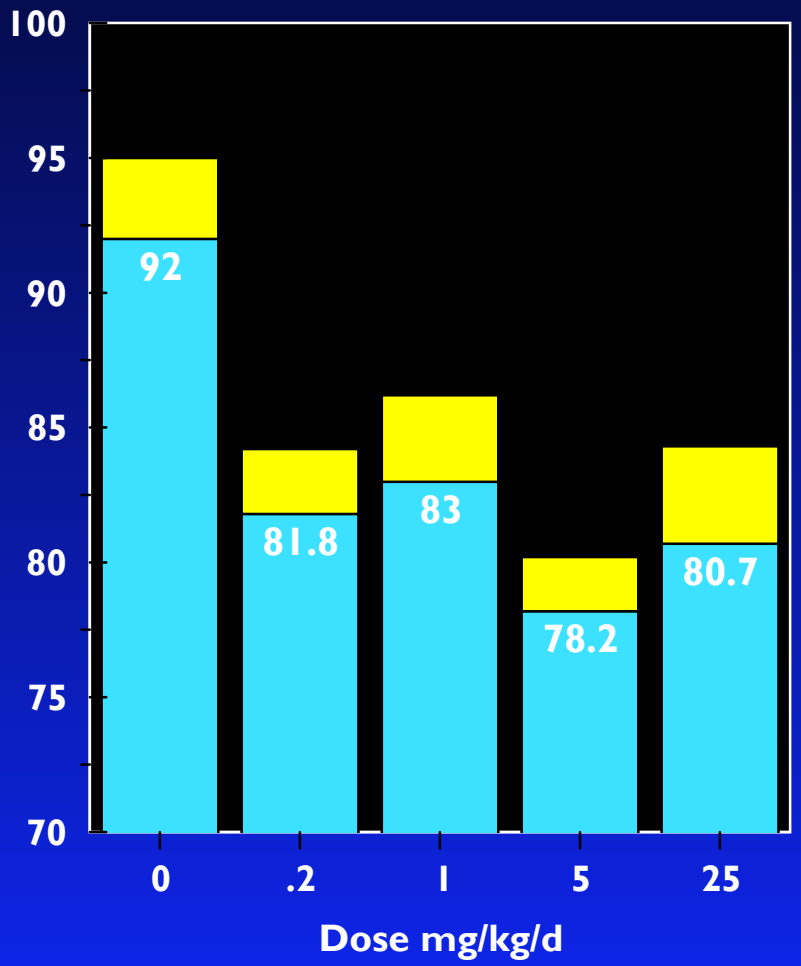


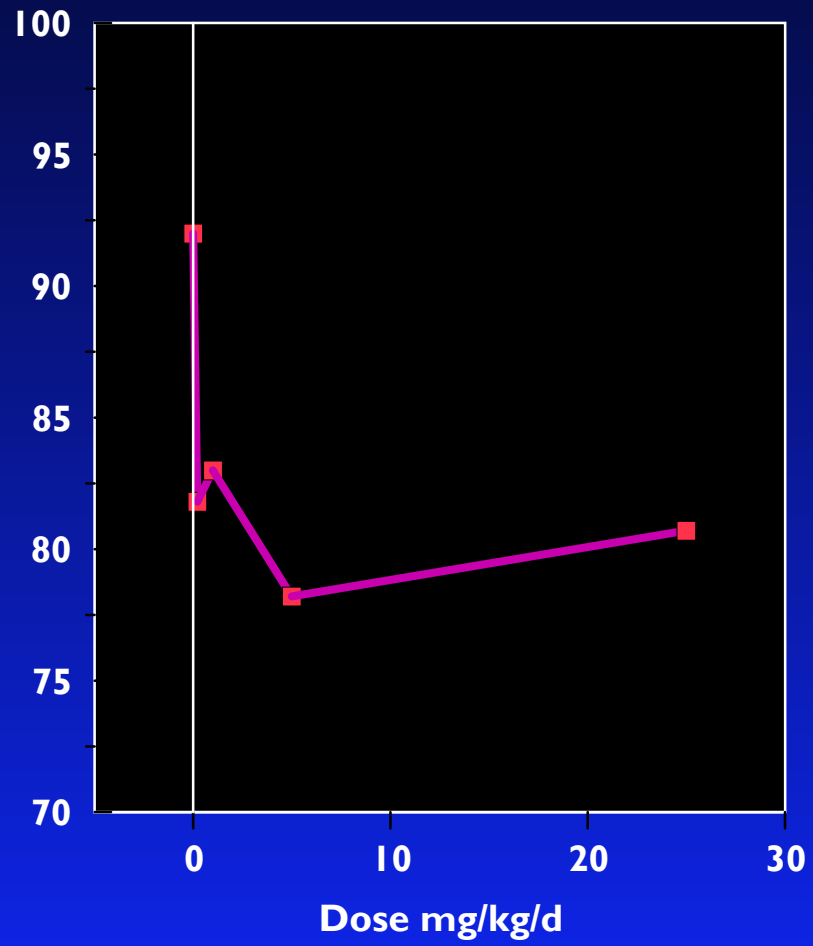


125. Effect of Finasteride on LABC weights. Data from four labs

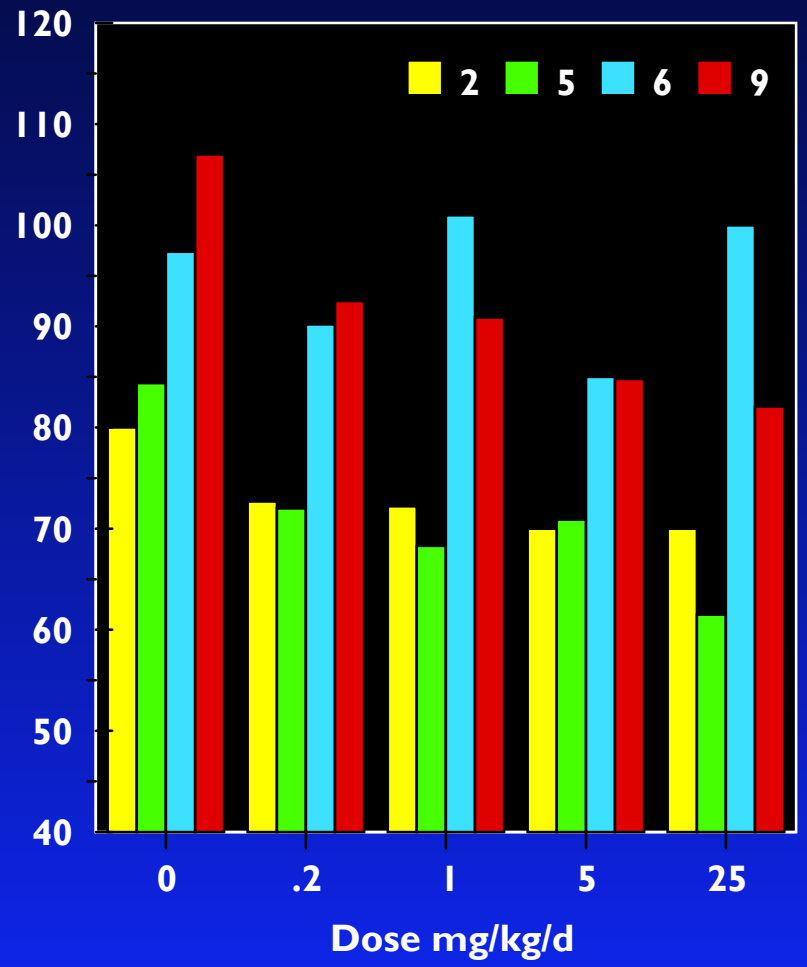


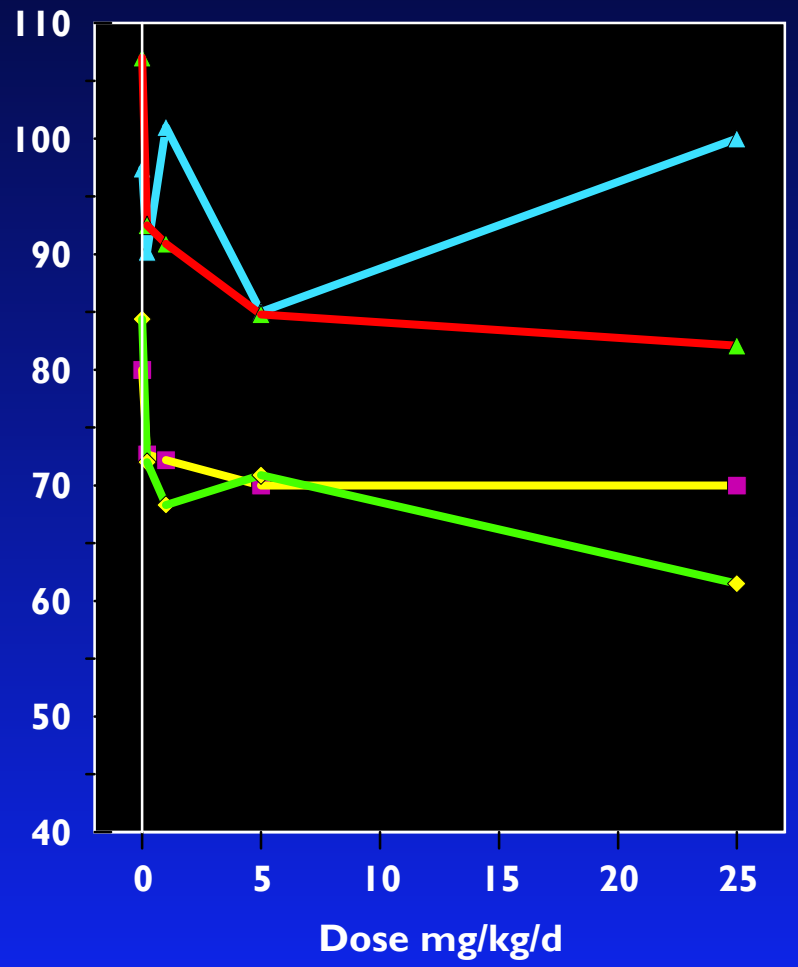
126. Effect of Finasteride on Glans penis weights. All values differ from control ($p<0.01$). Data from four labs



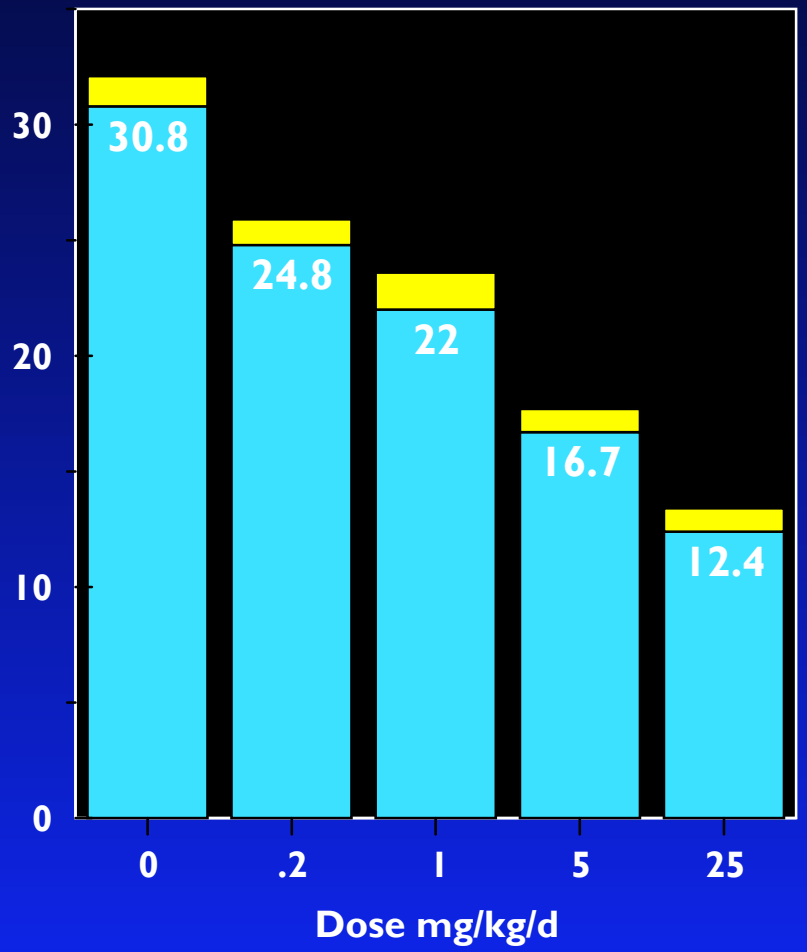


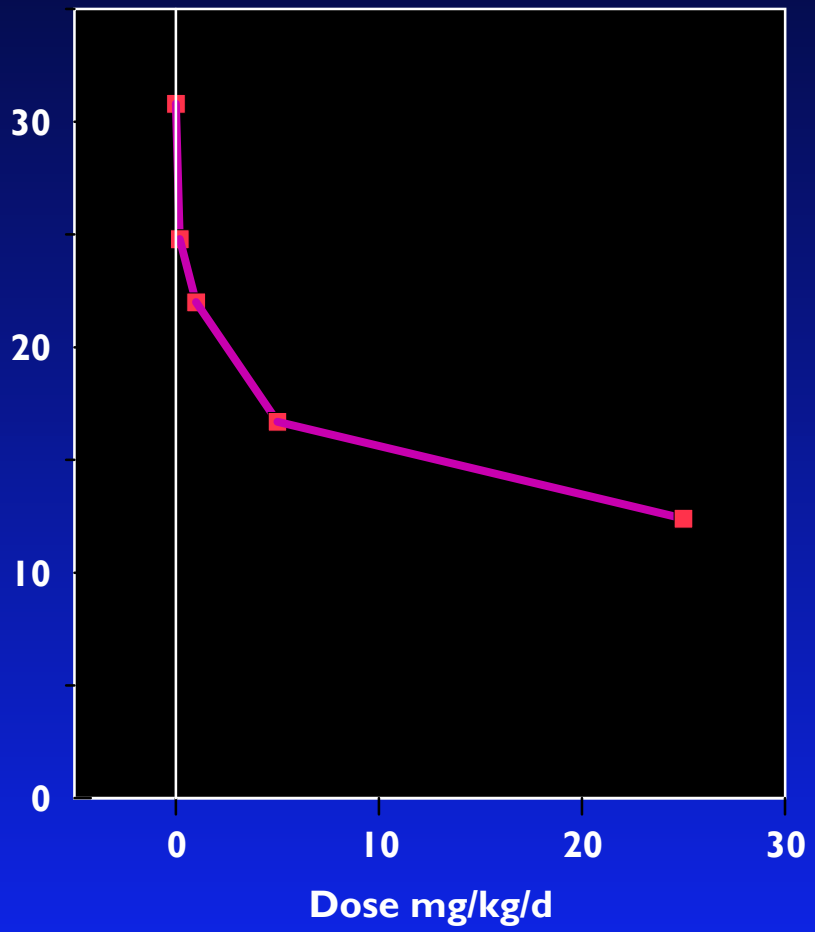
127. Effect of Finasteride on Glans Penis weights. Data from four labs



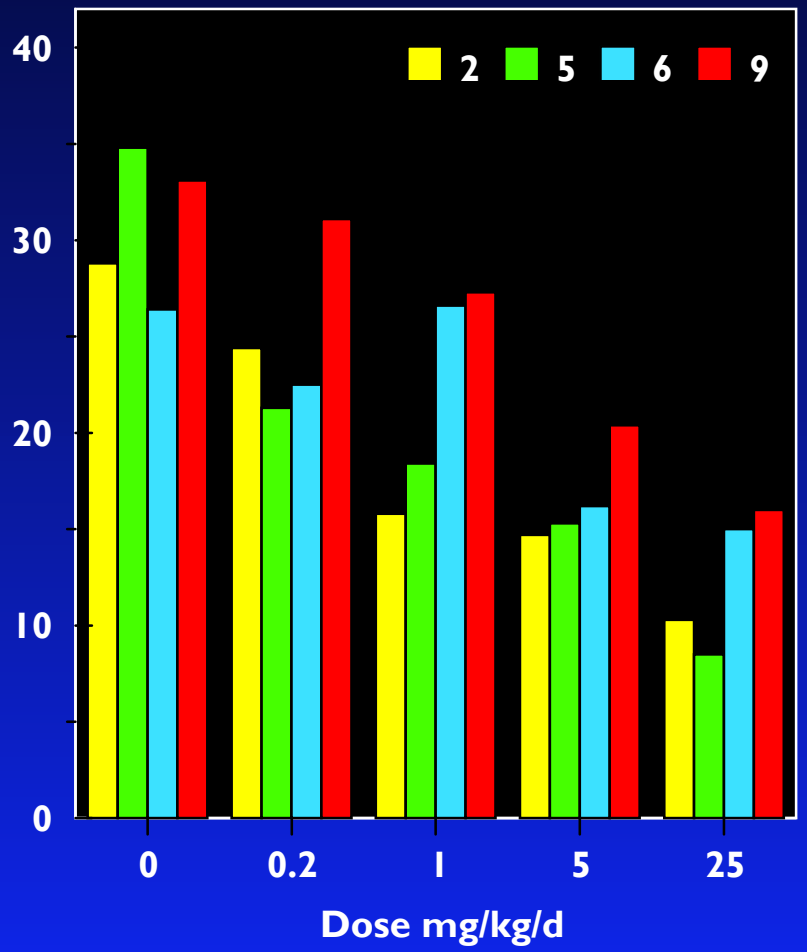


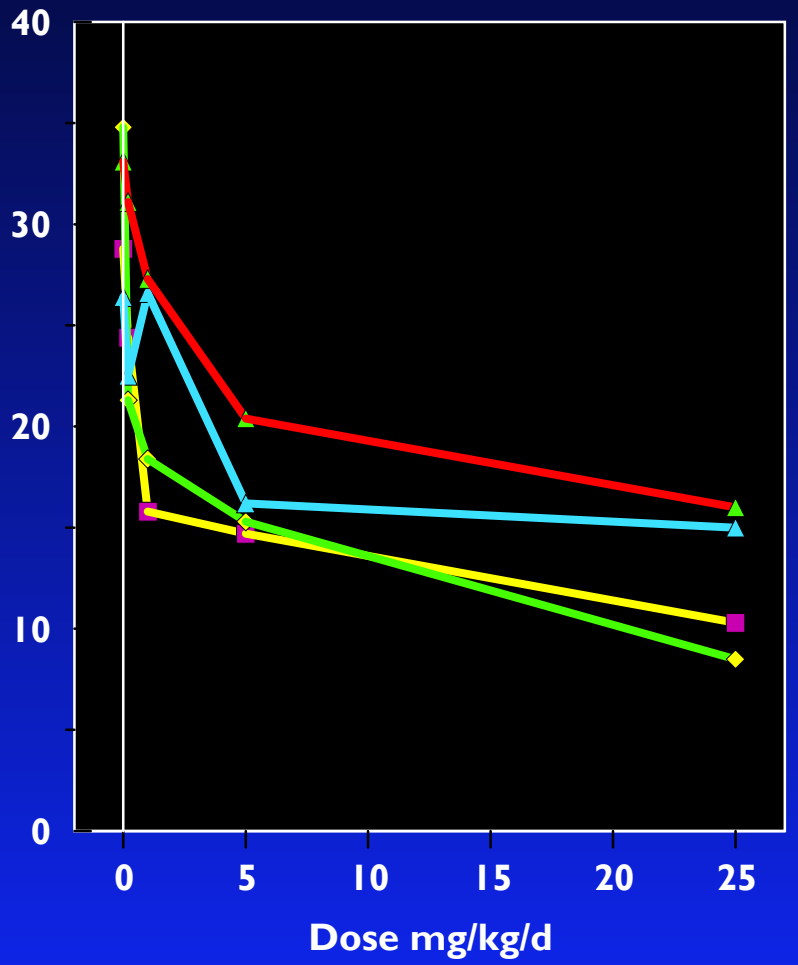
128. Effect of Finasteride on Cowper's gland weights. All values differ from control (p<0.01). Data from four labs



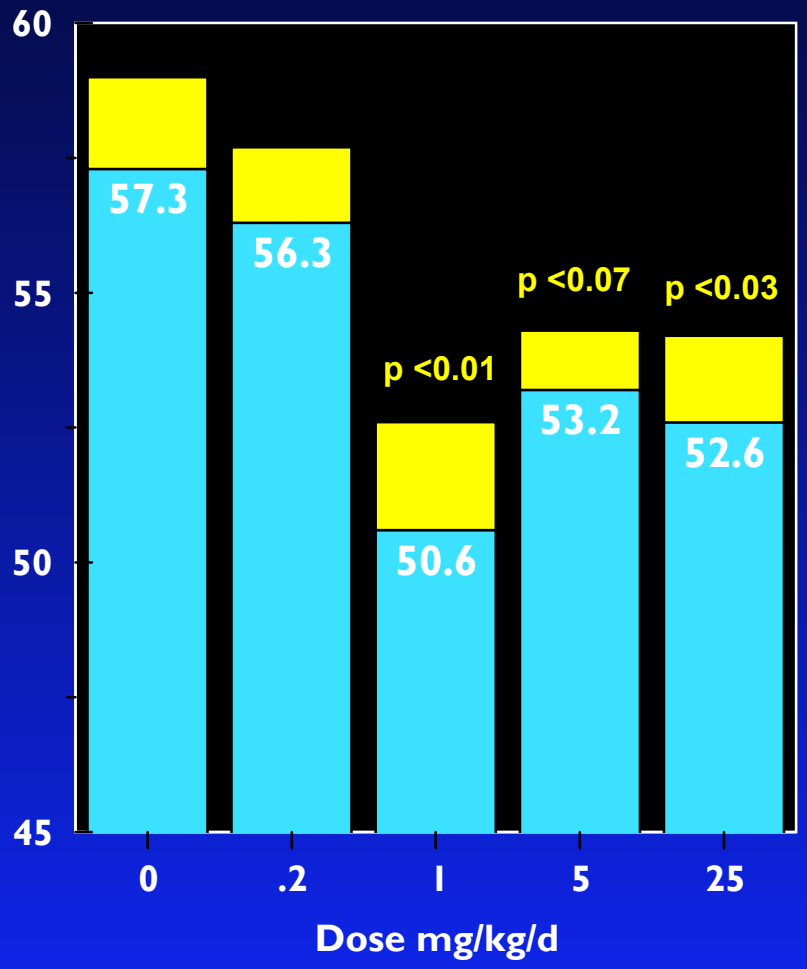


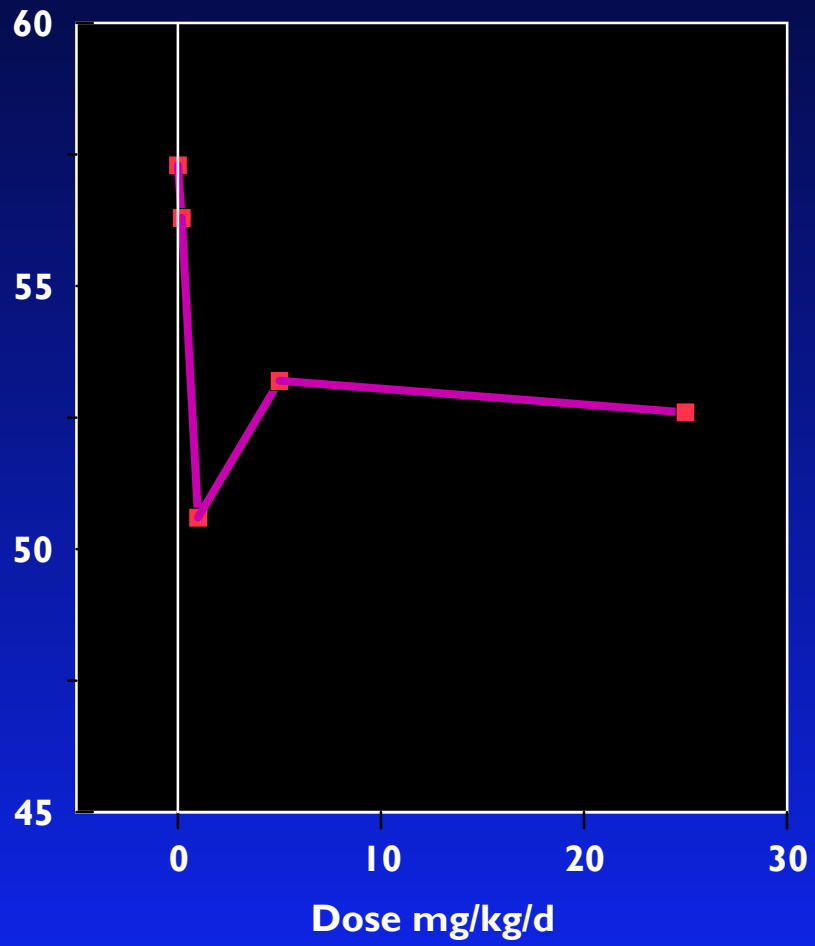
129. Effect of Finasteride on Cowper's gland weights. Data from four labs



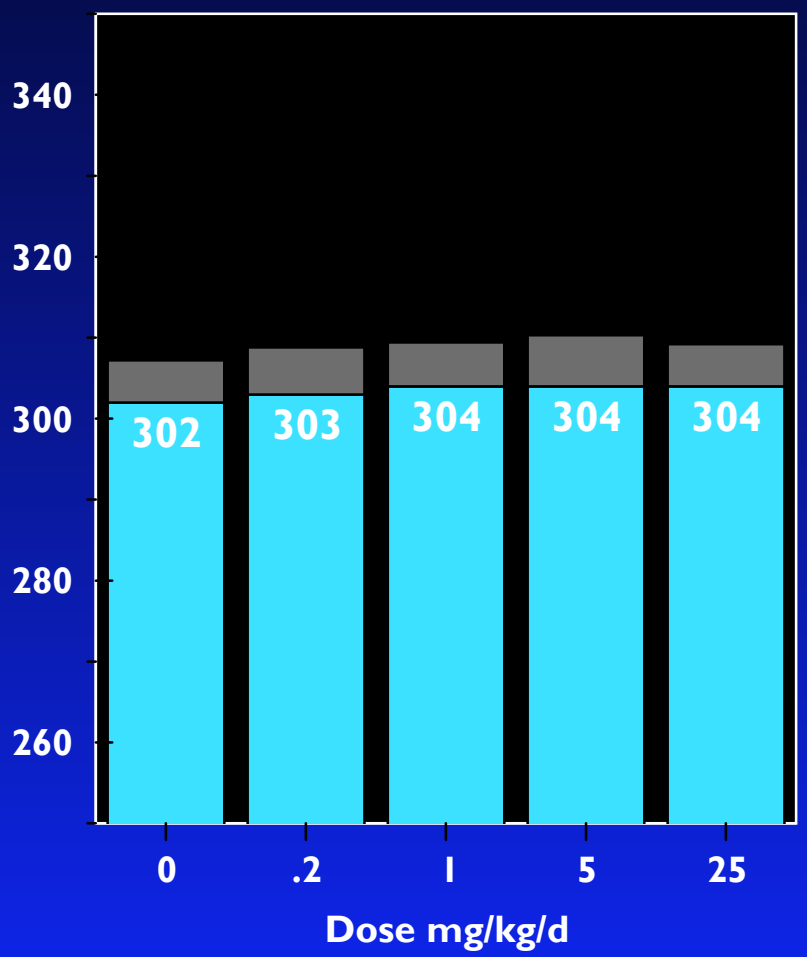


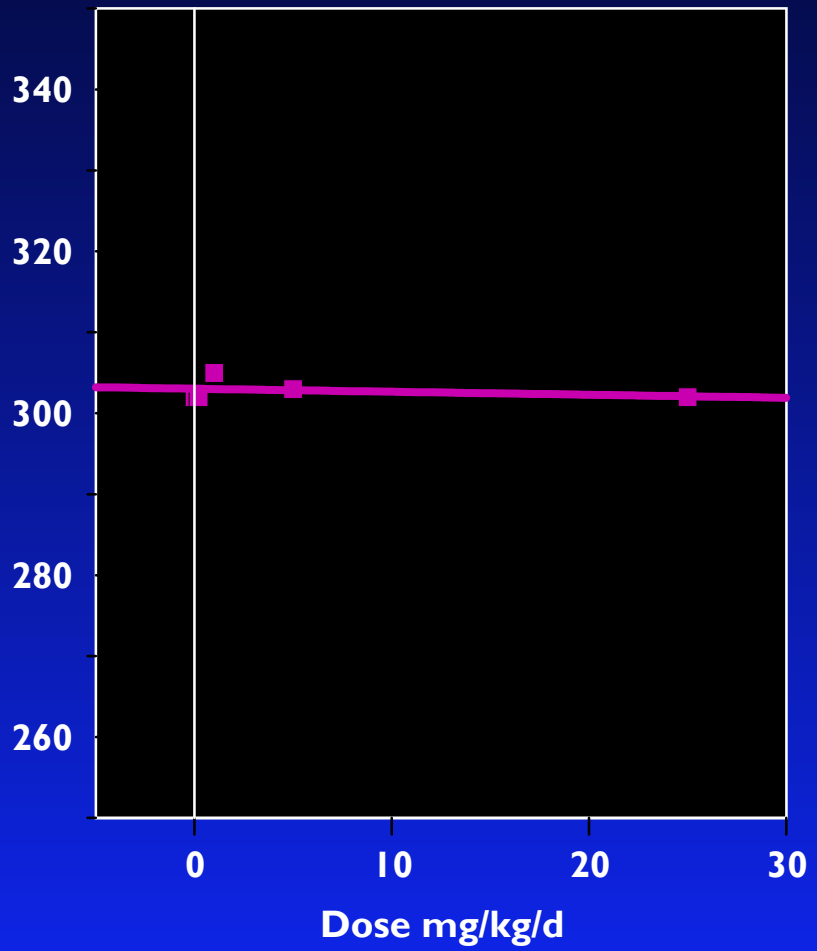
130. Effect of Finasteride on adrenal gland weights. Overall F=2.95, p <0.03. Data from four labs



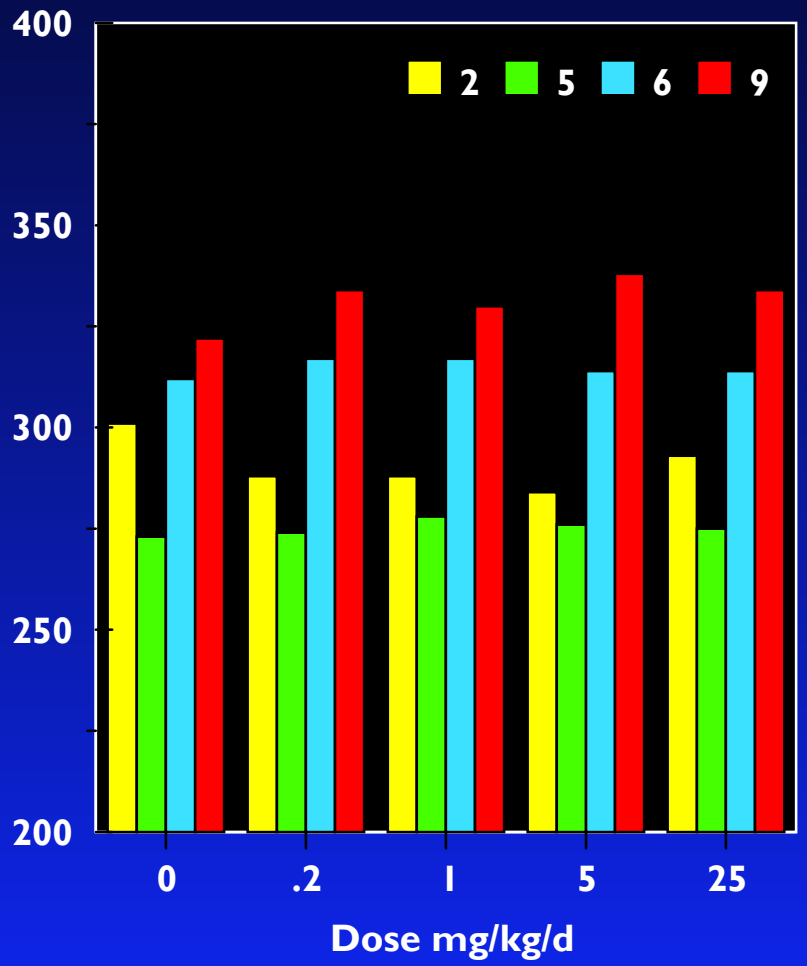


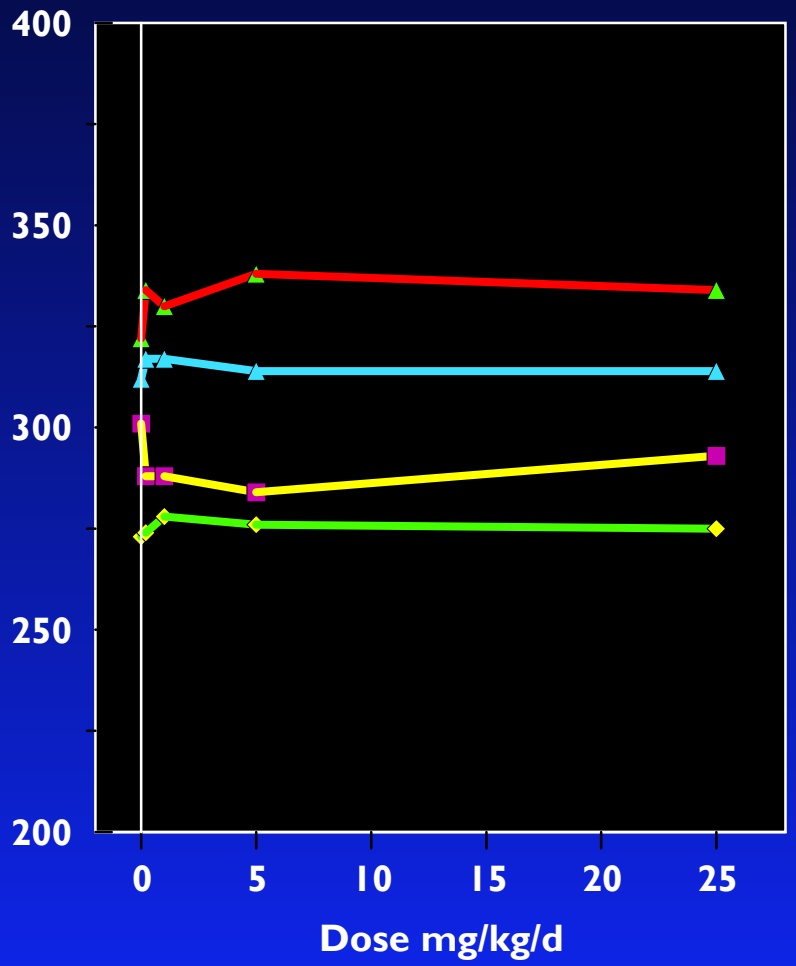
131. Lack of effect of Finasteride on Body weight at necropsy





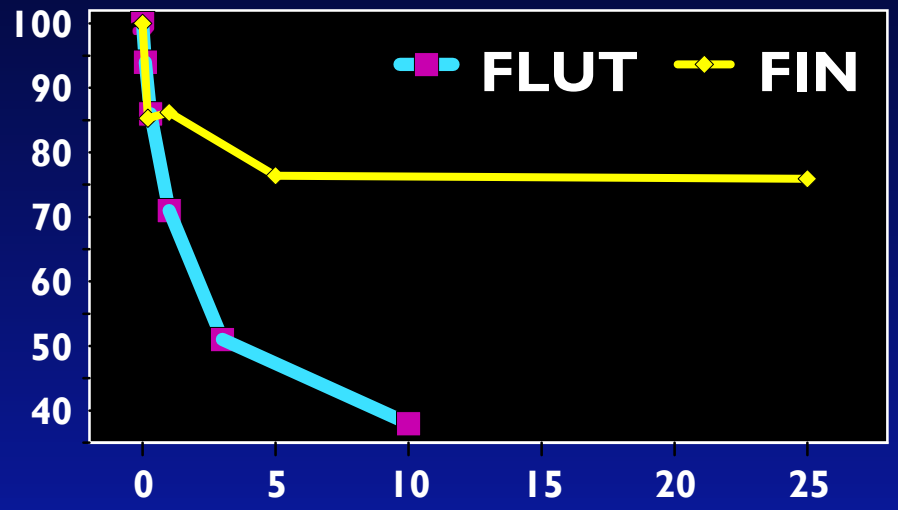
131b. Effect of Finasteride on Body weights. Data from four labs



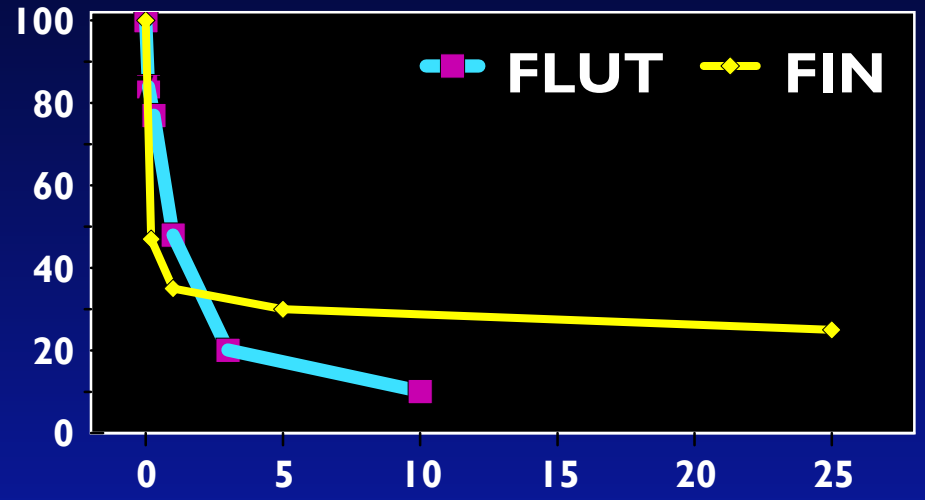


132. A Comparison of the Effects of finasteride and flutamide on androgen-dependent tissues weights in male rats treated with 0.4 mg TP/kg/d expressed as percent of TP control

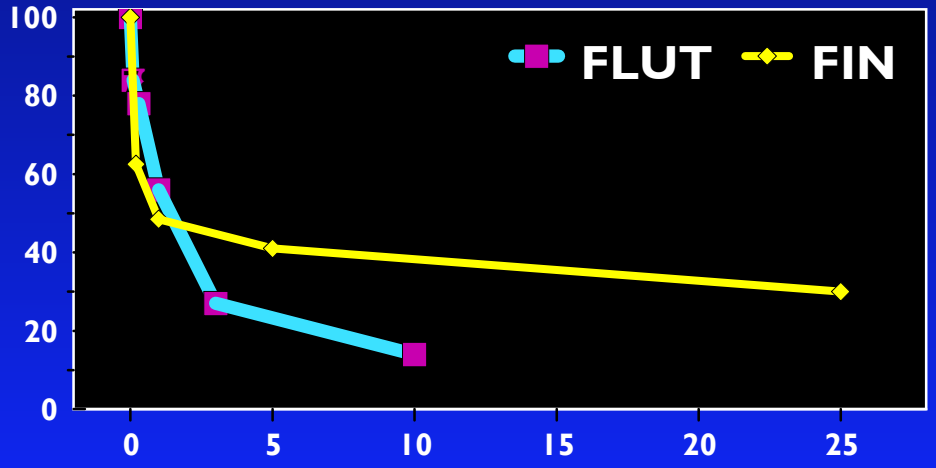
LABC



Seminal Vesicle



Ventral Prostate



Glans Penis