LINURON: COMPARING NOTIFIER’s *ALLEGED* TO THE INDEPENDENT LITERATURE’s *ACTUAL* L/NOAELs

I. Overall NOAEL, To Establish the Crucial ADI (DAR Sec. B.5B.5.10.2):

A. Based on Notifier’s data (with a desire to that linuron be authorized in order to make money):

0.9 to 1.3 mg/kg of b.w. d- was the no- or the lowest-dose that happened caused more than one effect:

- a NOAEL for reversible red blood cell toxicity in semi-chronic exposure tests in rats & dogs;

- a NOAEL for growth depression in reprotox tests;

- a LOAEL for a *decrease* in pituitary tumors; but taken as a toxic effect because it was in a D/R fashion and likely involved the LH/Testosterone hormones, which evidence shows Linuron distorts.

The latter effect, despite having not established a no-effect dose, was chosen to set the “safe” (ADI) dose. As the mechanism of the effect was not explicitly tested, an additional uncertainty factor of 5X was added to the usual ones for inter-species and inter-individual variation (overall UF = 500), leading to a proposed ADI of 0.003 mg/kg bw d- [Drinking water exposure was not explicitly tested, so an additional UF of 10X was added; so using in its place the feed exposure LOEL and assuming 2 L water intake per day leads to a proposed 9 ug/L MAC for drinking water.]

B. **However**, independent literature has falsified[[1]](#footnote-1) the ADI, showing it is *not* a protective, “Acceptable” daily intake:

The *decrease* in pituitary tumors with increasing dose better fits the hypothesis of low-dose hormone disruption than it does the DAR’s hypothesis of increasing & linear dose/response relations. Many endocrinologists note that hormones are more potent at low than at high doses, due to various biologic mechanisms such as the ‘spare receptor’ theory. In endocrinology, non-linear D/R curve results are too common to submit most of them for publication![[2]](#footnote-2) So when linuron caused more tumors at lower doses, via hormonal disturbance, the correct reaction would have been to continue testing at lower doses! In sum, linuron’s NOAEL was not approximated, therefore its ADI is false.

Since the DAR, published data (which the notifiers have presumably failed to notify their regulators about) has supported linuron’s anti-androgen testosterone suppression at lower doses than the ADI: In vivo vertebrate (female teleost fish) showed kidney cells with decreased protein spiggin, needed for testosterone production, at 150 ug/L of linuron for 21 days, well below the alleged LOEL.[[3]](#footnote-3) In vitro this team then found that spiggin can be inhibited by just 10(-10) M of linuron in cultured kidney cells—just 25 ng/L! (the abstract says 10(-14) M linuron = 2.5 pg/L).[[4]](#footnote-4)

Furthermore, the notifier’s hypothesis and submitted data, showing that only in adult animals does linuron cause leydig cell testicular tumors (via the non-genotoxic means of disturbing the HPT hormone axis), is faulty. Linuron is an established anti-androgen, as both the DAR and the independent literature show; and this class of agents has been shown, during several very precise windows, to disrupt several all-important biochemical pathways of male repdroductive development, from early pregnancy to post-natal.[[5]](#footnote-5) Yet hypothesis is never tested--no concurrent test of exposure during development was performed to meet the PPPDir’s requirements that no risk of pesticide exposure exist. This shows the need for more, not less, multi-generation reproductive and developmental toxicity assays.

Moreover, since the DAR, the independent literature has proven that anti-androgens such as linuron at much lower doses than the summarized in the DAR cause hormonal tumors, and many other male reproductive tract effects; at anti-androgen dose levels far lower than the notifiers ever tested or cited. Developmentally, the anti-androgen fungicide vinclozolin feminized several aspects of rat male reproduction at doses of 3.125 mg/kg b.w. d- and above--below its alleged NOAEL.[[6]](#footnote-6) Known estrogens increased fetal mice prostates (a cancer risk), including methoxychlor (which is also anti-androgenic) at 20 ug/kg d-.[[7]](#footnote-7)

The most-studied class of anti-androgens are phthalate esters. At dose levels just 100-fold more than average amounts found in human milk, the ubiquitous phthalate DEHP, also during the above-mentioned critical windows of development (which also reconciled conflicting results in other species), almost halved human sperm germ cells.[[8]](#footnote-8) At 10(-4) Moles, less than 10 X human body burdens, DEHP metabolites significantly disrupted several fetal rat whole-testis in-vitro functions.[[9]](#footnote-9) DEHP at human body burden level doses (0.135 mg/kg bw d-) during development disrupted aromatase, critical to determining sex hormone levels.[[10]](#footnote-10) DEHP & the phthalate DEP’s main metabolites were mutagenic to human sperm DNA at doses found in humans (confirming their earlier result for DEP).[[11]](#footnote-11)

The epidemiologic literature reinforces the experimental literature above, strongly and reliably associating human burdens of anti-androgen phthalates with male reproductive toxicity. An award-winning quality study associated such actual human levels of phthalates with several feminizations of boys, especially ano-genital distance (an utterly validated and life-long marker of mammalian feminizations[[12]](#footnote-12) (a result they and other researchers later confirmed; and human phthalate burdens have also been associated with early puberty in girls). Human sperm damage also is associated with phthalate levels, again later confirmed.[[13]](#footnote-13) Last, phthalates levels in human milk were associated with disruption of reproductive hormones towards feminization in human infants at three months.[[14]](#footnote-14)

As with many cumulative assessments, phthalate cumulative risk assessment showed cumulative risk when each individual phthalates was below its alleged NOAELs.[[15]](#footnote-15) Worse, in the real world vertebrates are exposed to many known and still unknown anti-androgens. Anti-androgen pesticide risks must be evaluated cumulatively!

II. Other Notifier’s Toxicity Data Later Falsified, and Data Gaps

**A)** **Genotoxcity**

[DAR Sec. B.5.4] The notifier’s hypothesized mechanism for their observed LOEL noted also that it is a non-genotoxic mechanism of action (i.e. increased leutenizing hormone leads to reproductive hormone imbalance and thus to tumors. The notifier’s and the DAR un-equivocably state that linuron is not genotoxic.

Yet just weeks after the DAR’s date, researchers independent of the notifiers monetary incentive to show safety published results showing that linuron was genotoxic directly (using the common MutaTox assay), and it was the most genotoxic of the ten pesticides after realistic metabolic (S9) activation: at 2 ug/L.[[16]](#footnote-16) Why has the notifier apparently never so notified EFSA of this data contradicting their claim—could it be their monetary interest? Genotoxicity can affect any function of life, not just cancer.

**B)** **Cancer**

Cancers were the LOAEL used to establish linuron’s proposed ADI, see DAR Sec. B.5B.5.10.2.

In the 1980’s—in a well-known review, available to the notifiers and agencies--linuron was estimated by eminent scientists to represent 98% of the cancer risk of herbicide residues in food.[[17]](#footnote-17) Food residue levels may have declined since the 1980’s, but this expert opinion still seems greatly at odds with EFSA’s opinion on linuron’s carcinogenicity. Likely, the DAR’s failure to recognize linuron’s genotoxicity helps explain why EFSA made the wrong conclusion on its carcinogenicity. Given that it is a genotoxin, its cancer risk must now be re-evaluated with data showing the cancer potency slope down to zero exposure (practically, extrapolated down to the dose that society accepts as a tolerable amount of cancer, typically one additional lifetime cancer per 100,000 or million people. Far more realistic risk assessment, however, is to dose the test animals throughout their life cycle and over a broader dose level.

**C)** **Neurotoxicity & Developmental Neuroto**x

[DAR Sec. B.5.7] Presumably the DAR’s “Delayed Neurotoxicity” reference means ‘chronic neurotoxicity. For that important health endpoint the DAR presents zero data; nor are there any developmental neurotox. studies.

Neither has the independent literature tested for linuron neurotoxicity. As with all other areas of health, the most vulnerable stage of life—development--must be tested before the notifiers of the agencies can claim linuron has met its mandate of no toxicity for authorized pesticides.

**D)** **Developmental/Reproductive toxicity**

[DAR Sec. B.5.6] It is remarkable that in multi-generation tests, the notifiers tests very often fail to find a no-effect dose (a NOAEL)--including the studies selected for the crucial overall ADI! Also no reason is given why the slightly more potent LOAEL found (12.5 ppm in feed, 0.9 mg/kg b.w. d-) was not used for establishing the ADI.

More important, linuron has both DAR-evaluated and DAR-ignored anti-androgenicity at high doses, and anti-androgens in utero have well-known potent effects on adult reproductive toxicity (we summarized this above). Therefore the notifier’s reported developmental tests are entirely inadequate. Dosing should begin before conception and continue, in stages, through development of the offspring!

In addition, other anti-androgens (including the fungicide vinclozolin) cause metabolic and other diseases *four generations after the exposed generation*, via both mutations and epigenentic changes to DNA[[18]](#footnote-18) (they have subsequently expanded those results). Reproductive development is one key area of DNA change causing these extended-generation findings, and linuron does disrupt reproductiion at high doses. The DAR utterly fails to test linuron’s multi-generation reproductive and other developmental effects at realistic doses.

**E) Immune Toxicity**

This organism-wide toxic endpoint is not once mentioned in the DAR!

Only one academic team has studied linuron’s immunotox (20 years ago in the USSR, so no dose levels are mentioned in the abstracts). They report that chronic, “small” linuron injections caused a “severe” immune deficiency syndrome in vivo.[[19]](#footnote-19) Clearly the notifiers were obliged to search the literature for this published result.

**F)** **Ecologic Effects**

[DAR Sec. B.8] The DAR notes that linuron is persistent in water, increasing chronic exposure risks. For fish, using toxicity to (predicted) exposure ratios (T:E R), the DAR estimates slight acute exposure risks and no significant chronic risks (although the test for chronic toxicity only tested adults for 21 days). 3.15 and 0.707 mg/L are the acute & semi-chronic LC50 (LOAEL) values used.

Since then, but unreported by the notifier, just ten minutes of linuron at 10 ug/L—about 100 times below the claimed LOAELs--more than halved salmonid’s olfactory response--olefaction is a subtle, indispensable sense for life in water, e.g. to find prey and avoid predation.[[20]](#footnote-20)

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For aquatic organisms (Daphnia magna being the most sensitive organism) the DAR estimates risks are greater than accepted (too low a T:E ratio) for both acute and chronic exposures, using LC50 LOAELs of 0.31 and 0.18 mg/L.

Yet, unreported by the notifier, a single application of linuron, from 10 nM to 1 mM (about 2.5 ug/L to 250 mg/L), thoroughly disrupted a freshwater aquatic ecosystem.[[21]](#footnote-21) Also, somewhere between 1 ng/L and 100 ug/L of several pesticides (including linuron), “typically less than their listed EC50 value”, decreased numbers of the aquatic indicator species Daphnia magma.[[22]](#footnote-22) Thus key aquatic ecosystem elements are disrupted by linuron at concentrations about 100 times lower than the DAR says is already a risk!

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With algae as the most sensitive species, the DAR estimates that linuron use causes severe acute risks to plants (based on 0.007 mg/L (i.e. 7 ug/L) EC50 LOAEL to algae); and it admits that there is no data to evaluate linuron’s chronic toxicity risk to plants.

Yet, unreported by the notifier, between 0.5 to 5 ug/L linuron for 11 weeks significantly decreased the primary productivity (photosynthesis) of a macrophyte (rooted aquatic plant) community.[[23]](#footnote-23) Thus, chronic (11 weeks, anyway) exposure to linuron is more deadly to plants than the DAR estimates the acute risk is!

**METABOLITE & IMPURITY RISKS**: 3,4-dichloroaniline (3,4-DCA); Tetrachloro-Azo/AzoOxy-Benzenes (TCAB, TCAOB)

[Throughout the DAR, especially Sec.’s B.2, B.3, B.4, B.5.13 ] In the DAR, none of these linuron-related chemical families’ exposure or risks are systemically studied. The notifier’s data says that 27% of the radioactive tracer-linuron metabolites in a vertebrate dosing study remain unidentified, and impurity data—both occurrence & toxicity--is kept secret, making it impossible to test the notifier’s massive financial motive to report safety no matter what the truth is.

3,4-DCA is briefly mentioned in analysis detection methods and toxicokinetics (ADME), only 3,4-DCA is studied further—but only for its presence in food residues and its effects on soil. Otherwise its toxicity is ignored. 3,4-DCA is a precursor for various petrochemicals, the herbicide propanil’s main metabolite, as well as being an impurity in Linuron and a minor metabolite.

No surprise (except to the notifiers, as they have failed to notify EFSA), 3,4-DCA has been found in humans at up to 6.19 ppm in urine, typically below 1 ppm.[[24]](#footnote-24) It is also widespread in the environment, and--once again un-notified by the notifier--3,4-DCA s very toxic to the aquatic ecosystem indicator species Daphnia magna: 6 ug/L (~ ppb) severely impacted its reproductive success,[[25]](#footnote-25) a result independently replicated at 5.9 ug/L.[[26]](#footnote-26) Even less 3,4-DCA—2 ug/L—but in combination with 40 ug/L of lindane, significantly decreased the growth of juvenile zebrafish.[[27]](#footnote-27) Thus 3,4-DCA is toxic at ppb levels, far below its levels in humans and other organisms. The need for cumulative risk assessment of 3,4-DCA could not be clearer.

The TCAB & TCAOB linuron impurities are structural analogues of perhaps the most potent synthetic chemical (other than plutonium), 2,3,7,8-TCDD (“dioxin”). Therefore their levels and toxicity are relatively well studied. Linuron as-sold contained about 1 – 10 ppm TCAB & TCAOB, in 1990--after some significant efforts to reduce its formation in linuron manufacture. They are also produced in related herbicides and when 3,4-DCA is manufactured; and when those products degrade & metabolize in the biosphere. No published data is apparently available on TCAB & TCAOB levels in humans, so the notifiers did not necessarily fail to notify EFSA, but the Ntl. Toxicology Program of the USA in studied their toxicity based on major concerns about human exposure.[[28]](#footnote-28) They are as potent as dioxin in inducing chloracne--a reliable biomarker of dioxin exposure.[[29]](#footnote-29) TCAB was from two to six orders of magnitude (i.e., 100 to a million) less potent at AhR induction than the most potent dioxin, 2,3,7,8-TCDD, the most potent toxin in the world—i.e. TCAB was a very potent (just 100 times less potent than 2,3,7,8-TCDD) cause of *some* of the many toxicities downstream from the induction of AhR (see the published NTP studies). For TCAOB, a similar wide spectrum of toxicities and no safe dose was found down to 100 ppb of body weight by feeding (see the published NTP studies); while various immune system alterations by TCAOB are caused by 1.4 – 3.6 ppb levels in chick eggs,[[30]](#footnote-30) close to the immunotoxicity of the most potent immunotox of dioxins. Thus the levels of this linuron impurity should be disclosed and their risk investigated, especially since some of the known toxicity data was published even before the literature was allegedly reviewed for the DAR.

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LINURON: Directive’s “zero risk” *claims* vs. the Independent Literature

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| *EFFECT* | *D.A.R.Claimed NOAEL*  | *Falsified by LOAEL* | *Factor LOAEL Below claimed NOAEL* |
|  |  |  |  |
| Genotoxicty |  Not genotoxic | 2 ug/L | Infinite-times! |
| Cancer | (see text) | (see text) | Potentially many-times (see text) |
| Chronic & Devel’l Neurotoxicities | Untested | none | Data Gap |
| Developmental & Reprod. toxicity | (see text) | (see text) | Potentially many-times (see text) |
| Immune Toxicity | Untested | Severe deficiency | Many-times (presumably) |
| LC50 Fish | Chronic: UntestedSemichronic 0,707 mg/L Acute 3,15 mg/L | UntestedUntested0,01 mg/L (acute) | Data Gap Data Gap315-times (& effect length unknown) |
| LC50 Daphnia | 0,31; 0,18 mg/L | 0,0025 mg/L | 72-times |
| EC50 Algae | 0,007 mg/L | 0,0005 mg/L | 14-times |
| Metabolite toxicity | Untested | 0.0059 mg/L(3,4-DCA)  | Human urine (many sources) ~1 mg/L! |
| Impurity toxicity | Untested | 1.4 ppb (internal dose) | AhR inducer, many potent toxicities. |

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1. This means ‘results overturned by subsequent tests’; not a accusation of fraud. However the DAR’s data is all from parties to whom objective toxicity testing of its products threatens hundreds of millions of Euros of revenue. [↑](#footnote-ref-1)
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