CENTER FOR FOOD SAFETY

February 6, 2017

Objections to EPA's establishment of tolerances for residues of dicamba in or on cotton, gin byproducts; cotton, undelinted seed; soybean, forage; and soybean, hay under 40 CFS Part 180. Final rule published in Federal Register, Vol. 81, No. 236, pp. 88627-88634

Docket ID Nos.: EPA-HQ-OPP-2010-0496 and EPA-HQ-OPP-2012-0841

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On December 8, 2016, EPA established the following tolerances for residues of the herbicide dicamba under 40 CFR Part 180.227:

- Cotton, gin byproducts: 70 ppm
- Cotton, undelinted seed: 3.0 ppm
- Soybean, forage: 60 ppm
- Soybean, hay: 100 ppm

Under the Federal Food, Drug and Cosmetic Act (FFDCA), the EPA may only establish a pesticide tolerance if that tolerance is safe, meaning "there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information," giving special consideration to protection of infants and children from harm.

EPA has not demonstrated that aggregate exposure to dicamba residues is safe. Therefore, the Agency should revoke the dicamba tolerances established by this final rule unless or until adequate toxicological data are available to make the requisite safety determination under the FFDCA. The reasons for this objection follow.

Neurotoxicity

EPA has failed to demonstrate, with reasonable certainty, that aggregrate exposure to dicamba residues will not cause neurological harm to infants and children. EPA finds that "[c]onsistent neurotoxic signs (e.g. ataxia, decreased motor activity, impaired righting reflex and gait) were observed in multiple studies [of dicamba] in rats and rabbits," as well as brain ventricular dilation in female rats.[1] For instance, when orally administered to

[1] EPA (3/29/16). Dicamba and Dicamba BAPMA Salt: Human Health Risk Assessment for Proposed Section 3 New Uses on Dicamba-Tolerant Cotton and Soybean. Health Effects Division, EPA, 3/29/16, p. 23.

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adult rats, dicamba (BAPMA salt) induced numerous symptoms of neurotoxicity, including unsteady gait, convulsions and ataxia; while the BAPMA salt itself, when administered to adult rats, induced labored respiration, piloerection, unsteady gait and semiclosed eyelids.[2] The most frequently reported symptoms in human incidents relating to exposure to dicamba and dicamba-containing products involved the nervous system.[3]

Despite this clear evidence of neurotoxicity in adult test animals and human beings, EPA failed to require a developmental neurotoxicity study to investigate the potential for neurological harms to infants and children from aggregate exposure to dicamba residues. Fetuses and infants are in general more susceptible to neurological and other harms from exposure to toxins at lower levels than adults. The Food Quality Protection Act of 1996 instructed EPA to protect infants from pesticidal harms by employing a 10X safety factor unless "reliable evidence shows that a different safety factor is protective of infants and children." In order to protect infants and children, the 10X safety factor lowers by a factor of 10 the maximum level of pesticide exposure regarded as safe for adults. The EPA did not apply any FQPA safety factor [i.e. EPA set the FQPA safety factor to 1X] in the case of dicamba, despite the lack of "reliable evidence" showing that aggregate exposure of infants and children to dicamba residues would not cause neurological harm.

The EPA has developed test guidelines for conducting developmental neurotoxicity studies that are specifically designed to assess pesticides for potential harm to the developing fetus and lactating infant by administering the pesticide to pregnant/maternal test animals.[4] Offspring thus exposed to the pesticide (*in utero* and via mother's milk) are then evaluated for neurological and behavioral abnormalities, motor activity, response to auditory startle and learning performance, among other endpoints. No other animal studies prescribed in EPA test guidelines and submitted to the Agency for dicamba assess these endpoints, or assess them adequately.

EPA scientists recommended in 1999 that "developmental neurotoxicity testing be included as part of the minimum core toxicology data set for all chemical food-use pesticides for which a tolerance would be set."[5] In the continuing absence of required tests for developmental neurotoxicity, EPA scientists have specified that such testing should be required if existing data demonstrate that the pesticide "cause[s] neuropathology in developing or adult animals or neuropathy in humans," while EPA-appointed scientific advisors have specified that "developmental neurotoxicity testing should be (a) mandatory if the substance has been shown to cause CNS [central nervous system] malformations;

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[2] EPA (3/29/16), op. cit., pp. 85-87.
[3] EPA (3/29/16), op. cit., p. 29.
[4] Health Effects Test Guidelines: OPPTS 870.6300 – Developmental Neurotoxicity Study. EPA 712-C-98-239, EPA, August 1998.
[5] Thayer K and Houlihan J. Pesticides, Human Health, and the Food Quality Protection Act, 28 Wm. & Mary Envtl. L. & Pol'y Rev. 257 (2004), p. 288. http://scholarship.law.wm.edu/wmelpr/vol28/iss2/3.

[and] (b) strongly considered if the substance has been shown to cause neuropathology/neurotoxicity in adults…"[6]

Although these criteria are clearly met for dicamba, EPA declined to apply any FQPA safety factor for dicamba, or to require submission of a developmental neurotoxicity study on dicamba. Thus, EPA cannot with reasonable certainty assert that aggregrate exposure to dicamba residues will not cause neurological harm to infants and children, and should revoke the dicamba tolerances at issue in this final rule.

Cancer

EPA has failed to demonstrate, with reasonable certainty, that aggregrate exposure to dicamba residues (including the metabolite 3,6-DCSA) will not cause cause cancer. Below, we discuss EPA's assessment of the carcinogenic potential of dicamba and 3,6-DCSA based on animal studies, human epidemiology, and mechanistic evidence of genotoxicity, one pathway to cancer. EPA's faulty assessment led to an incorrect dismissal of the carcinogenic potential of dicamba and its metabolite, 3,6-DCSA.

Animal studies

Two rodent studies provide evidence that dicamba causes malignant lymphomas and thyroid parafollicular tumors in male rats; and lymphosarcomas in female mice.[7] The cancer findings in these two studies are summarized in Tables 1 and 2.

Table 1: Rat Study – Tumor Results for Male Rats
(animals with tumors/total animals)

	Control	Low-Dose	Mid-Dose	High-Dose
Malignant lymphomas	0/60	0/60	4/60	4/60
Thyroid parafollicular cell carcinomas	1/60	0/60	2/60	5/60

Note: Dose levels 0, 2, 11 and 107 mg/kg bw/day for control through high-dose, respectively.

Table 2: Mouse Study – Tumor Results for Female Mice
(animals with tumors/total animals)

	Control	Low-Dose	Mid-Low Dose	Mid-High Dose	High-Dose
Lymphosarcomas	2/52	4/51	8/52	7/52	5/52

Note: Dose levels 0, 5.8, 18.8, 121 and 354 mg/kg bw/day for control through high-dose, respectively.

[6] Makris, S et al. (1998). A retrospective analysis of twelve developmental neurotoxicity studies submitted to the US EPA Office of Preventions, Pesticides, and Toxic Substances (OPPTS). Health Effects Division, EPA, 11/12/98, p. 46.

[7] Goldenthal, E. (1985) Lifetime Dietary Toxicity and Oncogenicity Study in Rats: Technical Dicamba: 163-694. Unpublished study prepared by International Research and Development Corp. 2101 p. MRID 00146150; and Crome, S.; Stuart, V.; Anderson, A.; et al. (1987) Dicamba: Potential Tumorigenic Effects in Prolonged Dietary Administration to Mice: Report No. VCL 72/871205. Unpublished study prepared by Huntingdon Research Centre Ltd. 966 p. MRID 40872401.

EPA's Guidelines for Carcinogen Risk Assessment describe two statistical tests to determine whether the observed cancers are plausibly attributed to the compound (here, dicamba) or to chance: trend test and pairwise comparison.[8] For all three cancers (two in male rats, one in female mice), the Cochran-Armitage trend test established a statistically significant trend of increasing tumors with rising dose. In the pairwise comparison test (Fisher Exact test), tumors in a treatment group are compared to those in the control group. The numbers of rats with each type of tumor were elevated in the high-dose group, but not to the level of statistical significance. However, the malignant lymphomas in male rats (high-dose 4/60 versus control 0/60) narrowly missed being a statistically significant increase ($p < 0.059$); and lymphosarcomas in the mid-low mouse group were significantly elevated versus the control.

According to EPA's Guidelines: "Significance in ***eithe***r kind of test is sufficient to reject the hypothesis that chance accounts for the result."[9] Thus, EPA violated its Guidelines by dismissing the tumors as not "toxicologically significant" because their incidence was significantly elevated in one but not ***both*** tests.[10]

Animal carcinogenicity trials must be conducted according to well-articulated test guidelines. A key requirement of these test guidelines is that: "The highest-dose level should elicit signs of toxicity without substantially altering the normal life span due to effects other than tumors."[11] This is a standard feature of protocols for animal carcinogenicity studies, and is referred to as the maximally tolerated dose, or MTD.[12] However, the high doses in the dicamba studies were too low, because they did not elicit such signs of toxicity in the animals that were fed them. With respect to the rat study, EPA stated: "Treatment had no adverse effect on survival, body weight, body weight gain, food consumption, hematology, clinical chemistry, urinalysis, organ weights or gross pathology." EPA concedes that the "lack of systemic toxicity" meant that "an MTD was not achieved."[13] Thus, "the doses tested in the rat and mouse carcinogenicity studies were inadequate for

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[8] EPA (2005). Guidelines for Carcinogen Risk Assessment. EPA/630/P-03/001F, EPA, March 2005, p. 2-19.
[9] EPA (2005), op. cit., p. 2-19, emphasis added.
[10] With respect to the male rat results: "The Cochran-Armitage trend test showed a statistically significant ($p < 0.05$) tendency for the proportion of animals with tumors to increase steadily with increase in dose. Pairwise comparison (Fisher's Exact test) showed no statistical significance. ***Therefore***, these tumors were not considered to be toxicologically significant" (EPA 3/29/16, p. 75, emphasis added).
[11] EPA (1998). Health Effects Test Guidelines: OPPTS 870.4200 – Carcinogenicity, EPA 712-C-98-211, EPA, August 1998, p. 4.
[12] See e.g. FDA (2008). Guidance for Industry: S1C(R2) Dose Selection for Carcinogenicity Studies. U.S. Food and Drug Administration, Revision 1, September 2008; NRC (1993). Issues in Risk Assessment. Committee on Risk Asssessment Methodology, National Research Council, National Academy Press, Washington, DC, 1993; Rahman MA and Tiwari RC (2012). Pairwise comparisons in the analysis of carcinogenicity data. Health 4(10): 910-918.
[13] EPA (3/29/16), op. cit., p. 74.

evaluating the carcinogenic potential of dicamba based on the lack of toxicity observed in those studies."[14]

EPA also considered a chronic toxicity/carcinogenicity study in which rats were fed the dicamba plant metabolite, 3,6-DCSA. This study also failed to incorporate a high dose that elicited "signs of toxicity" as required by EPA Test Guidelines, and so does not provide an adequate test of the carcinogenicity of 3,6-DCSA. According to EPA:

"There were no toxicologically significant treatment related effects on mortality, clinical signs, body weight, food consumption, ophthalmology, clinical chemistry, hematology, coagulation, urinalysis, or organ weights. There were no toxicologically significant effects noted for gross or microscopic pathology."[15]

The fact that none of the rodent carcinogenicity studies incorporated a maximally tolerated dose of dicamba invalidates the pairwise comparison test. The rationale for incorporating a maximally tolerated dose is to maximize the ability of the study to detect any carcinogenic effects the compound might have.[16] Thus, failure to use an MTD renders the study inadequate for assessment by the pairwise comparison test. Four of 60 rats (7%) fed the inadequate high-dose of dicamba had malignant lymphomas, while 5 of 60 (8%) had thyroid carcinomas. If the high dose had been the MTD, it is very likely that such an MTD group would have had a higher, statistically significant elevation in tumor-bearing animals versus the control group in the pairwise comparison test. This result is likely because there were statistically significant ***trends*** of increasing tumors with increasing dose in both studies, suggesting that MTD groups would have had more tumor-bearing animals than those in the inadequate high-dose groups. In this case, both studies would have shown statistically significant tumor elevations as measured by both tests rather than by the trend test alone, providing still stronger evidence of carcinogenicity.

In 2005, nearly two decades after the rodent cancer studies were submitted to EPA, and a decade after the studies were judged to be inadequate, the Agency re-evaluated them in light of additional pharmacokinetic/toxicokinetic data (PK data) that were submitted by the registrant, BASF Corporation. EPA now maintains that the PK data demonstrate that the high doses tested in the rodent feeding trials were in fact adequate to assess carcinogenicity.[17] This is not the case.

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[14] EPA (11/7/16). Response to public comments received regarding the new use of dicamba on dicamba-tolerant cotton and soybeans. Docket ID: EPA-HQ-OPP-2016-0187, EPA, November 7, 2016, p. 4, citing an internal EPA memo designated HED Doc 012037, 7/29/96.

[15] EPA (3/29/16), op. cit., p. 92. Note that EPA classified this study as "non-guideline," presumably because of the inadequate high dose.

[16] As per EPA Guidelines: "The high dose in long-term studies is generally selected to provide the maximum ability to detect treatment-related carcinogenic effects, while not compromising the outcome of the study through excessive toxicity or inducing inappropriate toxicokinetics (e.g., overwhelming absorption or detoxification mechanisms)" (EPA 2005, op. cit., p. 2-15).

[17] EPA (11-7-16), op. cit., p. 4, citing EPA internal memo TXR 0053647, dated 8/16/05.

According to EPA Guidelines, a dose that does not elicit signs of toxicity (i.e. is not an MTD) may still be excessive if it results in "saturation of absorption and detoxification mechanisms."[18] However, the high doses fed to male rats (107 mg/kg bw/day) and female mice (354 mg/kg bw/day) in the cancer studies did not even come close to saturating absorption mechanisms. One PK rat study cited by EPA (MRID 46022302) shows clearly that "absorption was not saturated, even at the highest dose" of 800 mg/kg bw/day,[19] nearly eight times the high dose in the rat carcinogenicity study. Neither does any PK data cited by EPA provide evidence that "detoxification mechanisms" were "saturated."[20]

Instead, EPA rests its case on PK data relating to "saturation of excretion," a parameter that is not mentioned in its Guidelines. However, even here EPA determined that "the dose levels in the chronic toxicity/carcinogenicity study in rats ***could have been higher*** based on kinetics data which indicated that saturation of excretion occurred at a dose ranging from >200 to 400 mg/kg/day,"[21] and that "definite saturation" only occurred at "400 mg/kg/day."[22] Assuming that saturation of excretion is a valid parameter for setting the high dose, the rat cancer study should have incorporated a dose of 400 mg/kg/day, nearly four times the high dose actually administered to male rats that developed malignant lymphomas and thyroid carcinomas (107 mg/kg/day).

Given the statistically significant trends for increasing lymphomas and thyroid carcinomas with rising dose observed in the rat study, one would clearly anticipate a still higher incidence of these cancers in rats fed an appropriate high dose of 400 mg/kg/day. In this case, these cancers would likely be found to be caused by dicamba treatment by both of the statistical tests (trend and pairwise comparison) prescribed in EPA Guidelines, rather than just one (trend). This would provide still stronger evidence of dicamba's carcinogenicity. As noted above, however, EPA Guidelines clearly state that the statistically significant trend result, alone, is sufficient to reject chance as an explanation for the observed tumors.

With respect to the rat study, EPA states that the observed malignant lymphomas and thyroid parafollicular (C-cell) carcinomas "are not uncommon and can occur spontaneously in aged CD-1 rats,"[23] implying that the cancers were not caused by dicamba. First of all, EPA does not cite any evidence to support this statement. Second, there is no "CD-1" strain of rat. CD-1 refers to the strain of mouse used in the mouse study; and the rat study

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[18] EPA (2005), op. cit., p. 2-17.
[19] EPA (3/29/16), op. cit., p. 78.
[20] Detoxification refers to processes by which the organism chemically alters the parent compound to render it non-toxic. Dicamba and its chief metabolite in dicamba-resistant plants, DCSA (3,6-dichlorosalicylic acid), are for the most part excreted unchanged in urine (EPA 3/29/16, p. 20), indicating that little or no detoxification takes place, and that any detoxification mechanisms that are active would not be saturated.
[21] EPA (3/29/16), op. cit., p. 75, emphasis added.
[22] EPA (11/7/16), op. cit., p. 5.
[23] EPA (11/7/16), op. cit., p. 5.

employed the "CD" (shorthand for Crl:CD(SD)) strain of Sprague-Dawley rats.[24] Third, both cancers are in fact relatively uncommon in male Crl:CD(SD) rats, even aged rats, and thus are unlikely to have occurred "spontaneously."[25] Thus, contrary to EPA, the high incidences observed in the studies are likely due to dicamba treatment, as indicated by the trend data.

EPA also justifies the high dose of 107 mg/kg/day (males) as adequate based on the lack of adverse effects in other toxicity studies at doses below the saturation point of 400 mg/kg/day. Yet the two studies EPA refers to are: 1) Subchronic studies in which dicamba was fed to rats for only 90 days (one-eighth the length of the 24-month carcinogenicity studies); and 2) Not designed to test the carcinogenicity of dicamba.[26] Hence, they provide no support for 107 mg/kg/day as an adequate high dose, and no evidence that dicamba is not carcinogenic.

EPA also maintains that the chemical structure of dicamba suggests it has low potential to be carcinogenic, referring to the OncoLogic Cancer Expert System.[27] However, this System is not mentioned in EPA's Guidelines for Carcinogen Risk Assessment, and does not provide evidence to refute the rodent studies that do provide evidence of cancer. In fact, neither of OncoLogic's uses as stated on EPA's website properly apply to this dicamba assessment. These uses are: 1) To assist industry in early R&D stage screening of candidate chemicals; and 2) To assist the Agency in assessing potential cancer concerns of "existing chemicals ***for which cancer bioassay data are not available***."[28]

With regard to the mouse study, EPA illegitimately dismissed cancer findings in females that were statistically significant by two measures: a significant pairwise difference in lymphosarcomas between the mid-low dose group (8/52) and controls (2/52), and a trend of increasing lymphosarcomas with rising dose. EPA dismissed these findings due to 1) Lack of a "clear monotonic dose-response;" 2) Historical control data suggesting that the

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[24] EPA (9/13/05). Dicamba: HED Chapter of the Reregistration Eligibility Decision Document (RED) – Phase I. PC Code 029802; DP Barcode D317720, EPA, 9/13/05, pp. 49-50. "CD" is an abbreviated designation for the rat strain Crl:CD(SD), where CD(SD) refers to "caesarian derived" (CD) in 1955 from original Sprague-Dawley (SD) rat colonies maintained by Charles River laboratories (Crl). See White and Lee (1998). The development and maintenance of the Crl:CD(SD)IGS BR rat breeding system. Biological Reference Data on CD(SD)IGS rats – 1998. Charles River Publications, p. 14.
http://www.crj.co.jp/cms/cmsrs/pdf/company/rm_rm_a_igs_rat_breeding_system.pdf , p. 14).

[25] Data from Charles River Laboratories on spontaneous tumors in Crl:CD(SD) rats in two-year studies show that the relevant tumors are relatively uncommon: "lymphocytic lymphomas" (a category that includes malignant lymphoma AND lymphocytic leukemia) occur spontaneously in only 1.7% of male Crl:CD(SD) rats; while thyroid parafollicular cell carcinomas (aka thyroid C-cell carcinomas) occur spontaneously in only 1.4% of male Crl:CD(SD) rats. See Charles River (2004). Compilation of spontaneous neoplastic lesions and survival in Crl:CD (SD) rats from control groups. Prepared by Mary L.A. Giknis, Charles B. Clifford. Charles River Laboratories, March 2004, pp. 6, 16, 17.

[26] EPA (11/7/16), op. cit., p. 5.

[27] EPA (11/7/16), op. cit., p. 5.

[28] See EPA's description of OncoLogic at https://www.epa.gov/tsca-screening-tools/oncologictm-computer-system-evaluate-carcinogenic-potential-chemicals. Last visited 2/3/17.

significant lymphosarcoma findings were due to an unusually low incidence in the concurrent controls.[29]

First, EPA Guidelines say nothing about monotonic dose-response as a criterion of significance for tumor findings, and instead prescribes a statistical trend test. Second, the significance of the historical control data is unclear, and not dispositive, for several reasons.

a) EPA Guidelines make it clear that the tumor data from concurrent controls takes precedence over that from historical controls: "The standard for determining statistical significance of tumor incidence comes from a comparison of tumors in dosed animals with those in concurrent control animals."[30]
b) EPA Guidelines state: "statistically significant increases in tumors should not be discounted simply because incidence rates … in the concurrent controls are somewhat lower than average."[31] (EPA 2005, p. 2-21). EPA dismissed the significant pairwise comparison on precisely these grounds, stating that it "was likely due to the lower than expected spontaneous incidence of this tumor type in concurrent controls."[32]
c) EPA does not report the average (mean) incidence of lymphosarcomas in the pooled historical control groups, which provides the best estimate of spontaneous occurrence. Without this average (mean), it is impossible to judge whether or not the incidence of lymphosarcomas in the concurrent controls is an acceptable standard of comparison.
d) EPA reports only the range of lymphosarcoma incidence rates in individual historical control groups. EPA Guidelines state: "Caution should be exercised in simply looking at the ranges of historical responses, because the range ignores differences in survival of animals among studies and is related to the number of studies in the database."[33] EPA does not report the number of historical control groups, their size or the survival rates of control animals.
e) Historical control data should not only be from derived from studies conducted in the same laboratory where the carcinogenicity trial was carried out, but from studies conducted within 2 or 3 years of the cancer trial, and with animals obtained from the same supplier.[34] EPA does not report this information.

<u>Other considerations relating to the biological significance of cancer in animals</u>
The human significance of animal tumor findings is increased when the tumor type is uncommon, and when the tumors are malignant rather than benign.[35] Both the lymphomas

[29] EPA (11/7/16), op. cit., pp. 5-6.
[30] EPA (2005), op. cit., p. 2-20.
[31] EPA (2005), op. cit., p. 2-21.
[32] EPA (11/7/16), op. cit., p. 6.
[33] EPA (2005), op. cit., p. 2-20.
[34] EPA (2005), op. cit., p. 2-21.
[35] EPA (2005), op. cit., pp. 2-21, 2-22.

and thyroid cancers are relatively uncommon, if not rare, in Crl:CD(SD) rats (see footnote 25). Significantly, all of the identified neoplasms were malignant rather than benign. EPA ignored these important considerations in its interpretation of the animal data.

Human epidemiology studies

A number of epidemiology studies provide evidence that exposure to dicamba is associated with higher incidence of cancer in farmers and pesticide applicators. Of note is a Canadian study[36] that EPA concedes provides such evidence in relation to the immune system cancer non-Hodgkin lymphoma.[37] However, EPA fails to provide an integrated assessment of the animal and human evidence, both of which point to the same cancer type. According to EPA's Guidelines: "epidemiological studies that show elevated cancer risk for tumor sites corresponding to those at which laboratory animals experience increased tumor incidence can strengthen the weight of evidence of human carcinogenicity."[38] Malignant lymphomas were found at statistically elevated levels in dicamba-treated male rats, while lymphosarcomas (an outmoded term for a cancer now also designated as malignant lymphoma) were statistically elevated in female mice, while the malignant cancer non-Hodgkin lymphoma is found at increased rates in dicamba-exposed farmers. EPA fails to weigh this important evidence of common cancer type in animal and human studies, which greatly strengthens the case that dicamba is indeed carcinogenic.

Mutagenicity

EPA maintains that dicamba is not genotoxic (i.e. does not cause damage to DNA), one pathway to cancer, relying primarily on studies submitted by dicamba registrants. Yet dicamba has clearly exhibited genotoxic properties in a number of open literature studies, summarized below.

Dicamba technical induced mutations in Salmonella typhimurium strains TA1535 without plant activation and in strains TA1538 and TA100 with plant activation; and it also induced mutations in Saccharomyces cerevisiae strain D4 after activation with rat-liver S9 microsomes.[39] EPA was aware of these tests because it supplied the researchers with technical grades of some of the herbicides they tested.

Dicamba induced DNA damage in both the Bacillus subtilis H17/M45 rec assay and the E. coli polA (W3110) assay.[40]

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[36] McDuffie, H. H., Pahwa, P., McLaughlin, J. R., Spinelli, J. J., Fincham, S., Dosman, J. A., Robson, D., Skinnider, L. F., & Choi, N. W. (2001). Non-Hodgkin's Lymphoma and specific pesticide exposures in men cross-Canada study of pesticides and health. Cancer Epidemiology Biomarkers & Prevention, 10(11), 1155-1163.

[37] EPA (11/7/16), pp. 30-32.

[38] EPA (2005), op. cit., pp. 2-2, 2-3.

[39] Plewa MJ et al. (1984). An evaluation of the genotoxic properties of herbicides following plant and animal activation. Mutation Research 136: 233-245.

[40] Leifer Z. et al. (1981). An evaluation of tests using DNA repair-deficient bacteria for predicting genotoxicity and carcinogenicity: a report of the U.S. EPA's Gene-Tox Program. Mutation Research 87: 211-297.

Dicamba induced DNA damage in human lymphocytes in vitro by means of unscheduled DNA synthesis (UDS) activity and in the liver of rats in vivo, and also stimulated sister chromatid exchange (SCE) frequency in human lymphocytes.[41]

Dicamba and a commercial formulation (Banvel) induced sister chromatid exchange in Chinese hamster ovary (CHO) cells at higher frequencies vs. controls at all concentrations from 1.0 to 500 ug/ml. Dicamba induced DNA damage in CHO cells in the single gel electrophoresis (comet) assay at concentrations ranging from 50 to 500 ug/ml, with similar results for the Banvel formulation.[42]

Though not all mutagenicity/genotoxicity assays of dicamba were positive, there are enough positive findings to suggest genotoxic potential. In particular, the positive genotoxicity results in human lymphocytes supports both the animal and human evidence for corresponding cancers of the lymphatic system.

REQUEST FOR FEE WAIVER

CFS requests that pursuant to 40 C.F.R. § 180.33(l), EPA waive all fees in connection with the filing of the objections and the request for fee waiver. In deciding whether the fee waiver criteria is satisfied, CFS respectfully reminds EPA it is the Administrator's sole discretion that such a waiver will promote the public interest. See 40 C.F.R. § 180.33(l). CFS is a 501(c)(3) nonprofit environmental advocacy organization that works to address the impacts of our food production system on human health, animal welfare, and the environment. CFS works to achieve its goals through grassroots campaigns, public education, media outreach, and litigation. In no manner does CFS have financial interest in any action requested, hence, a waiver of fees is appropriate here.

[41] Perocco P. et al. (1990). Evaluation of genotoxic effects of the herbicide dicamba using in vivo and in vitro test systems. Environmental and Molecular Mutagenesis 15: 131-135.
[42] Gonzalez NV et al. (2007). The chlorophenoxy herbicide dicamba and its commercial formulation Banvel induce genotoxicity and cytotoxicity in Chinese hamster ovary (CHO) cells. Mutation Research 634: 60-68.