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4 **COMMITTEE ON THE CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER**
5 **PRODUCTS AND THE ENVIRONMENT**

6

7 **Carcinogenicity of mixtures**

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9 Members are asked for comments on the first draft of a statement on the carcinogenicity
10 of chemical mixtures, which has been prepared by the DH Toxicology Unit.

11

12 Secretariat

13 March 2009

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17 **COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS**
18 **AND THE ENVIRONMENT (COC)**

19

20 **FIRST DRAFT STATEMENT ON THE ASSESSMENT OF THE CARCINOGENICITY OF**
21 **CHEMICAL MIXTURES**

22 1. At the horizon scanning exercise in 2007 it was suggested that we review current
23 developments in the assessment of chemical mixtures with regard to carcinogens, potential
24 interactions and their modes of action. A number of papers were prepared and presented.
25 Following an initial discussion paper in which general principles and examples were provided,
26 further papers examined the potential for chemical interactions in the carcinogenic process and
27 the synergistic effects of alcohol and tobacco, and of tobacco and asbestos.

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29 2. Interactions between compounds in a mixture, as detailed in the COT report 'Risk
30 Assessment of Mixtures of Pesticides and Similar Substances' (COT 2002), have been
31 classified as follows:

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- 33 1. Simple similar action (non-interaction, dose addition)
- 34 2. Simple dissimilar action (non-interaction, response addition)
- 35 3. Interaction (synergism/potentialiation or antagonism/inhibition)

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37 A group of chemicals which elicit their effects by the same mechanism or mode of action are
38 termed a common mechanism group (CMG). Their combined effects can be estimated by using
39 Toxic Equivalency Factors (TEF) which expresses the potency of each member of the group
40 relative to that of an 'index compound'. TEFs are used to standardize the hazard associated
41 with each chemical within the group. The class of compounds for which this method is most
42 widely used are the polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans
43 (dioxins). With regard to the carcinogenicity of dioxins, a few studies are available which
44 broadly demonstrate the concept of dose additivity for a CMG when using tumours as the
45 endpoint (Walker et al 2005) but the database is very limited.

46

47 3. Oestrogens may also form a CMG and there are some approaches using *in-vitro*
48 screening which provided robust information on dose additivity (Charles et al 2002, Payne et al
49 2001). However, there is a paucity of studies investigating *in vivo* responses to mixtures of
50 oestrogens. Moreover, there can be exceptions to the concept of dose additivity. For example,
51 oestrogens may act through either ER α or ER β to produce either inhibitory or stimulatory
52 effects.

53

54 4 We examined the potential of chemicals to interact synergistically at different stages in
55 the carcinogenic process. The following points in the carcinogenic process were identified as
56 examples of potential sites for interaction: ADME processes, DNA adduction, mutagenicity,
57 early preneoplastic changes, and neoplastic transformation. The literature was reviewed for
58 examples of interactions, examining in the first instance groups of chemicals such as polycyclic
59 aromatic hydrocarbons (PAHs) and heterocyclic amines (HCAs).

60
61 5) The COM, in its review of mixtures, has assessed papers according to the criteria laid
62 out in Borgert (2001). The essential criteria were:

- 63
- 64 1. Dose-response relationships for the individual mixture components are adequately
65 characterised.
- 66 2. An appropriate non-interaction or additivity hypothesis should be, a priori, explicitly
67 stated and used as the basis for assessing combination effects.
- 68 3. Combination of mixture components should be assessed across a sufficient range of
69 concentrations and mixture ratios to support the goals of the study
70

71 However, this was not considered appropriate for the papers we reviewed as the requirement
72 for detailed dose response data was usually not met. To accurately evaluate the potential
73 interactions of chemicals during the entirety of the carcinogenic process would necessitate life-
74 time carcinogenicity studies including groups to determine dose responses for the individual
75 chemicals as well as the combinations. This would result in large and complex studies.
76

77 6 The most widely investigated class of chemicals are PAHs, which includes complex
78 mixtures such as those found in coal tar and urban dust particulate matter. *In vitro* and *in vivo*
79 approaches were used in these papers to assess potential synergistic responses, including: the
80 production of DNA adducts, tumour formation using initiation promotion models and effects on
81 the cytochrome P450 (CYP) family of enzymes, particularly 1A1 and 1B1. There was some
82 evidence that some PAHs, including those within a complex mixture, may have the potential to
83 decrease the potency of others by altering metabolism. For example, a significant reduction of
84 DNA binding was observed when coal tar extract (Standard Reference Material, SRM₁₅₉₇) was
85 co-administered with benzo[a]pyrene (B[a]P) and dibenzo[a,l] pyrene (DB[a,l]P. In human
86 breast epithelial cells (MCF-10A), this was associated with induction of CYP1A1 and 1B1
87 (Mahadevan et al 2005). In V79 cells expressing CYP 1A1 or 1B1, the effect was more
88 apparent in the CYP1B1 expressing cells (Mahadevan et al 2007). EROD activity indicated that
89 SRM competitively inhibited the activity of both isoforms, more strongly on 1B1. *In vivo*,
90 SRM₁₅₉₇ reduced the number of tumours induced by DB[a,l]P in a SENCAR mouse skin model,
91 but did not have the same effect on B[a]P induced lesions (Marston et al 2001).
92

93 7. The studies provided some examples of how chemicals, including complex
94 environmental mixtures, can impact on the carcinogenic potential of other PAHs. In testing the
95 hypothesis of competitive inhibition of enzymes responsible for the metabolic activation of PAHs
96 it was broadly demonstrated that tumour promotion and DNA adduction were affected by the
97 mixtures and that this could be in part explained by altered CYP expression. For example, it is
98 proposed that B[a]P is more readily activated by CYP1A1 than by 1B1, such that the
99 competitive inhibition of this isoform would result in reduced activity. Furthermore, it was
100 suggested that the effects of environmental mixtures on the metabolism of DB[a,l]P differs from
101 B[a]P although this is not supported by all the available data. This probably indicates the
102 complexity of the interactions, both metabolic and genotoxic, involved in the processes and the
103 dose dependency of these interactions.
104

105 8. However, there are many reservations with regard to interpreting these data. Although it
106 is known that PAHs are inducers of xenobiotic metabolism, the extent of the induction would be
107 largely dependent on dose, dose route and tissue examined and differences between results
108 obtained *in vitro* and *in vivo* are often observed. The relevance of the SENCAR mouse skin
109 model for the evaluation of carcinogenicity is also questionable, as it is essentially a genotoxicity

110 assay. As such, it is difficult to extrapolate the altered risk of chemicals observed in the models
111 used and the implications for human risk assessment are uncertain. Additionally, it is
112 questionable whether CYP activity actually drives carcinogenic risk *in vivo*, as it is known that
113 effects are still seen in aryl hydrocarbon receptor knockout mice. Analysis of *in vivo* studies with
114 regards to potential interactions is difficult since pathways of metabolism, activation and
115 detoxification are inextricably linked and it is difficult to separate toxicokinetic interactions from
116 interactions downstream in the carcinogenic process.

117
118 9. Heterocyclic amines (HCAs) were also identified as a class of chemicals which have the
119 potential to interact with one another. A number of studies were retrieved which had assessed
120 potential interactions of food heterocyclic amines using liver foci initiation promotion models.
121 The HCAs examined were Trp-P-1, Glu-P-2, IQ, MeIQ and MeIQx, Trp-P-2, Glu-P-1, MeAaC,
122 AaC and PhIP (see Abbreviations). For example, these were administered as 1/1, 1/5, 1/10,
123 1/25 or 1/100 of the given dose (the known carcinogenic dose) and as combinations of all 5 at
124 1/5 and 1/25 of the dose or all 10 at 1/10 and 1/100. GST-P-positive foci >0.1mm were the
125 selected endpoint (Ito et al 1991, Hasegawa et al 1994 a,b). It was claimed that some HCAs
126 may act synergistically in promoting tumours through a hypothesised CYP induction mechanism
127 and this was apparent at low doses claimed to be relevant to a human consumption scenario.
128 However, it is difficult to draw useful conclusions from the studies on mixtures for a number of
129 reasons. Firstly, the initiation-promotion study protocols which have been used to examine
130 interactions between the HCAs were overly complex. The partial hepatectomy protocol fixes
131 mutations occurring during the period of regrowth and, since there was no consistent synergistic
132 response in this very sensitive model, the relevance to human health is questionable. The way
133 in which the authors have analysed the results (subtracting a high background incidence from
134 the induced incidence) is likely to be subject to significant error. In addition to the high variability
135 and high background tumour incidence, only limited dose response data was provided. No null
136 hypothesis was given and, therefore, no statistical comparison of the tested hypotheses was
137 possible. We do not agree with the conclusion from these studies that there was clear evidence
138 of synergy.

139
140 10. From the interaction studies we have examined, we conclude the following:
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142 • The terminology should more accurately reflect the interaction between the biological
143 responses resulting from exposure to the individual chemicals rather than use the term
144 chemical interaction which implies a reaction between chemicals.
145 • There can be apparent synergy at doses close to the threshold for effect but that this
146 would not necessarily be apparent at higher doses.
147 • The studies which evaluated HCAs were unconvincing.
148 • With regard to recommendations for future research; it is suggested that less complex
149 protocols might lead to more informative studies.

150
151 11. As a further part of the review we also decided to consider examples of interactions
152 between chemicals in the induction of cancer in epidemiology studies which may be of
153 significance to public health. Two sets of chemicals were selected: alcohol and tobacco, and
154 tobacco and asbestos, and we reviewed the extent of evidence for synergism and potential
155 mechanisms of interaction.

156
157 12. Alcohol and tobacco are known to be predominant risk factors for a number of cancers,
158 i.e. cancers of the mouth, neck and squamous cell carcinoma of the oesophagus. The studies

159 reviewed show that these two factors act in a greater than additive manner to produce these
160 cancers with effects apparent at moderate as well as high intakes (Lagergren et al 2000, Lee et
161 al 2007). However, this synergism is not apparent for oesophageal adenocarcinoma and
162 cancers of the gastric cardia (Sjodahl et al 2006).

163
164 13. The mechanism for the synergistic effect is not well understood and we considered a
165 number of plausible hypotheses. Firstly, the induction of cytochrome P450 (CYP) enzymes by
166 ethanol is suggested as a potential mechanism. There is evidence to indicate that ethanol
167 induces CYP isoforms which are capable of metabolically activating some carcinogenic
168 nitrosamines found in tobacco smoke. Induction of the 2E1 isoform at extra-hepatic sites such
169 as the oesophagus, combined with decreased first pass metabolism of tobacco associated
170 nitrosamines in the liver due to competitive inhibition by ethanol, is predicted to lead to
171 increased concentrations of DNA-reactive nitrosamine metabolites leading to elevated cancer
172 risk (Lecheveral et al 1999, Godoy et al 2002, Anderson et al 1995). A second hypothesis, for
173 which there are limited but convincing data *in vitro*, suggests that alcohol increases the
174 permeability of the oral mucosa to carcinogenic nitrosamines, which would account for the
175 synergistic effect observed (Du et al 2000, Azzi et al 2005).

176
177 14. We agree that the metabolic interaction hypothesis is plausible. However, it was
178 concluded that although the permeability mechanism looked reasonable, it was not clear
179 whether the *in vitro* results could be extrapolated to the *in vivo* situation. It is proposed that
180 consideration should also be given to the interaction of alcohol and growth factors and the effect
181 of local irritation of tissues. Also, although the metabolic argument is convincing, this scenario
182 could also be true of exposures to other chemicals which induce CYP2E1 and there are no
183 indications that there are similarly other synergistic interactions with alcohol.

184
185 15. Cigarette smoking and asbestos exposure both cause lung cancer and it has been
186 claimed that combined exposure results in a synergistic effect on lung cancer induction (Selikoff
187 et al 1968, Lee 2001). The exact nature of the interaction between asbestos and tobacco
188 smoking in the induction of lung cancer has been debated among researchers. From the
189 published literature, most systematic reviews have found a marked heterogeneity in the
190 magnitude of the joint effect, with the interaction ranging from less than additive in some studies
191 to more than multiplicative in other studies. Despite extensive investigations exploring the
192 interactive effects between cigarette smoke and asbestos, the precise mechanisms involved at
193 the cellular and molecular level are unclear. Asbestos and tobacco are both complex
194 carcinogens affecting more than one stage of carcinogenesis and may have interdependent
195 effects on the multistage process of lung cancer (Vainio and Boffetta, 1994).

196
197 16. A number of authors have proposed a synergistic interaction between cigarette smoke
198 and asbestos and various mechanisms have been proposed as the potential explanation.
199 These include:

- 200 • cytotoxic, genotoxic and clastogenic nature of asbestos and tobacco smoke – supra-
201 additive effects have been noted for mutation frequency, sister chromatid exchange, and
202 DNA strand breaks in a variety of test systems (Lohani et al 2002, Kelsey et al 1986,
203 Jung et al 2000)
- 204 • the generation of oxidative damage - both cigarette smoke and asbestos fibres generate
205 reactive oxygen species and synergistic responses in models evaluating this have been
206 observed. However mechanistic insights or hypotheses into this interaction are not well
207 developed.

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- enhancement of the penetration and accumulation of asbestos in the lung by tobacco smoke – demonstrated in a number of models including following the assessment of asbestos fibres in the airways of smokers and non-smokers (McFadden et al 1986 a,b).
 - the potential for asbestos to act as a delivery system for tobacco carcinogens into the lung, for example by enhancing the diffusion of lipophilic carcinogens (Gerde et al 1994), was shown to be unlikely.
 - the enhancement of somatic mutations in k-ras, FHIT and p53 genes. – some associations of smoking and/or asbestos exposure and lung cancer with these genes have been postulated although specific mechanisms have not been not described.

218 17. It is difficult to draw conclusions from these studies as the interaction models need to be
219 studied in depth to understand whether the interaction is additive or multiplicative and to
220 evaluate in detail the hypothesised mechanisms for the interactions. The definition of additivity
221 in an experiment appears to depend upon which model fits the individual chemicals evaluated.
222 Furthermore, the importance of different types of asbestos needs to be addressed; different
223 types of asbestos may fit different dose response models. Exposure misclassification might
224 also lead to substantial uncertainty in epidemiological studies; this distortion in risk estimates
225 means it is impossible to differentiate between interaction models. We consider that the
226 evidence is insufficient to preclude the null hypothesis, although there's some evidence that
227 there might be a synergistic interaction. It should be noted that, whilst mesothelioma risk stays
228 constant over time following cessation of exposure, lung cancer risk reduces in reformed
229 smokers. This probably reflects the fact that tobacco smoke is both an initiator and promoter of
230 cancer.

231

232 18. Overall, without an understanding of the specific mechanisms, it is hard to interpret the
233 short term studies presented; although it is possible to suggest plausible hypotheses.
234 Epigenetic mechanisms may also play a part, or asbestos exposure might increase uptake of
235 carcinogens from tobacco smoke. We consider that examination of the p53 mutational spectra
236 might offer some insights, as this is well defined for mutations arising as a result of exposure to
237 tobacco smoke. It might also be interesting to examine the anatomical location of lung tumours,
238 for example at bifurcations of the airway, which might help elucidate a mechanical mechanism.

239

240 19. Conclusions

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242 Overall, we reached the following conclusions in the discussion of mechanisms by which
243 chemicals may interact during the carcinogenic process,;

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- Mixtures of chemicals acting via the same mechanism, such as dioxins, can be assessed using the concept of dose additivity.
 - There are several potential sites for interaction between carcinogens in the carcinogenic process, for example, ADME processes, DNA adduction, mutagenicity, early preneoplastic changes, and neoplastic transformation.
 - It could be postulated that the combination of a chemical which causes a mutation with one that induces proliferation will act synergistically with regards to the induction of tumours

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- It also should be considered likely that otherwise non-carcinogenic chemicals, such as anti-apoptotic chemicals or chemicals interfering with cell cycle regulation, altering ADME processes or increasing permeability of skin/oral mucosa, might reasonably be expected to synergise with classical carcinogens.
 - It was considered that there were a number of possible ways to proceed in this area. Unfortunately, the assessment of potential interactions in the context of carcinogenicity is complex due to the multi-stage nature of the process and the high cost of carcinogenicity studies.
 - *In vitro* studies of interactions must be hypothesis driven, attempt to characterise the dose-response and use models relevant to *in vivo* carcinogenicity. These studies should adhere to the criteria laid out in Borgert et al (2001). Models used to evaluate the synergistic interactions between PAHs and HCAs were, in general, overtly complex and may not truly reflect the situation for carcinogenesis. Thus extrapolation for risk assessment in man is difficult.

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367 General Abbreviations:

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369 ADME = absorption, distribution, metabolism, excretion

370 B[a]P = benzo[a]pyrene;

371 CMG = common mechanism group

372 COM = Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment

373 COT = Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

374 CYP = cytochrome P450;

375 DB[a,l]P= dibenzo[a,l] pyrene;

376 DNA = deoxyribonucleic acid;

377 ER = oestrogen receptor

378 EROD = ethoxy resorufin-o-deethylase

379 GST-P = glutathione-S-transferase-placental

380 HCA = heterocyclic amine

381 MCF-10A = a human breast epithelial cell line;

382 SRM₁₅₉₇ = coal tar extract Standard Reference Material,

383 TEF = toxic equivalency factor;

384 V79 = a Chinese hamster cell line

385

386 HCA Abbreviations:

387

388 Trp-P-1 = 3-amino-1,4-dimethyl-5*H*-pyrido[4,3-*b*]indole,

389 Trp-P-2 = 3-amino-1-methyl-5*H*-pyrido[4,3-*b*]indole,

390 Glu-P-1 = 2-amino-6-methyl-dipyrido[1,2- α :3',2'-*d*]imidazole,

391 Glu-P-2 = 2-amino-dipyrido[1,2- α :3',2'-*d*]imidazole,

392 IQ = 2-amino-3-methylimidazo[4,5-*f*]quinoline

393 MeIQ = 2-amino-3,8-dimethylimidazo[4,5-*f*]quinoline,

394 MeIQx = 2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline,

395 MeAaC = 2-amino-3-methyl-9*H*-pyrido[2,3-*b*]indole,

396 AaC = 2-amino-9*H*-pyrido[2,3-*b*]indole,

397 PhIP = 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine