3. Recommendation for Exposure-Based Assessment of Joint Toxic Action of the Mixture

Lead, arsenic, cadmium, and chromium are frequently found together in the soil of hazardous waste sites. Although the monitoring data for hazardous waste do not usually distinguish between chromium(VI) and chromium(III), but rather are for total chromium, the form of concern is chromium(VI). The primary route of concern for a mixture of these chemicals in soil is likely to be oral, and the duration intermediate to chronic. Chronic exposure is of particular concern because of the cumulative nature of cadmium injury to the kidney, and the association of chronic oral exposure to arsenic with dermal lesions and cancer.

These metals probably constitute an incidental mixture at most waste sites where they co-occur. The components vary in concentration and in proportion to each other from one hazardous waste site to another, and one point of exposure to another. The ideal basis for the assessment of joint toxic action of this (or other) environmental mixtures would be data and models of joint toxic action for the toxicity and carcinogenicity of the complete mixture or validated PBPK/PD models that would support prediction of the effects of different doses and proportions of mixture components.

As discussed in Section 2.3, no adequate epidemiological or toxicological studies and no PBPK models are available for the quaternary mixture. A drinking water study of a mixture of lead, cadmium, and chromium(VI+III) in diethylnitrosamine-initiated rats gave no evidence of promoting activity for the mixture (Benjamin et al. 1999). Results of an intermediate-duration dietary study of toxicity and interactions for lead, arsenic, and cadmium in rats (Fowler and Mahaffey 1978; Mahaffey and Fowler 1977; Mahaffey et al. 1981) indicated that effects of the trinary mixture generally reflected those for the binary mixtures, suggesting that components-based approaches that focus on interactions for the binary mixtures may be useful in predicting the toxicity of the mixture.

In addition, although mechanisms for hematological effects are different for lead and cadmium, subthreshold exposures to these metals in combination resulted in significant decreases in hemoglobin and hematocrit (Mahaffey and Fowler 1977; Mahaffey et al. 1981; Thawley et al. 1977) suggesting that a health assessment approach that deals with each metal separately may underestimate the potential for mixtures of these metals to cause effects. Epidemiological studies of children have indicated that lead

and arsenic, and lead and cadmium, may interact at environmental levels of exposure to produce adverse neurobehavioral consequences in children (Marlowe et al. 1985a; Moon et al. 1985).

Because suitable data, joint action models, and PBPK models are lacking for the complete mixture, the recommended approach for the exposure-based assessment of joint toxic action of this mixture is to use the hazard index method with the TTD modification and qualitative WOE method to assess the potential consequences of additive and interactive joint action of the components of the mixture. These methods are to be applied only under circumstances involving significant exposure to the mixture, i.e., only if hazard quotients for two or more of the metals equal or exceed 0.1 (Figure 2 of ATSDR 2001a). Hazard quotients are the ratios of exposure estimates to noncancer health guideline values, such as MRLs. If only one or if none of the metals have a hazard quotient that equals or exceeds 0.1, then no further assessment of the joint toxic action is needed because additivity and/or interactions are unlikely to result in significant health hazard. As discussed by ATSDR (1992, 2001a), the exposure-based assessment of potential health hazard is used in conjuction with biomedical judgment, community-specific health outcome data, and community health concerns to assess the degree of public health hazard.

The TTD modification of the hazard index requires the estimation of endpoint-specific (target-organ-specific) hazard indexes for the endpoints of concern for a particular mixture. The endpoints of concern are neurological, dermal, renal, hematological, and cardiovascular. Although less sensitive than these endpoints, testicular effects also are potentially of concern because they are caused by lead, cadmium, and chromium(VI), and the joint action of lead and cadmium on this endpoint is synergistic. Therefore, these endpoints are candidates for TTD development for the components of this mixture. Because only arsenic causes dermal effects (basis for chronic oral MRL) after oral exposure, dermal TTDs were not developed for the other metals. The TTDs were derived as described in the Appendices to this document, using the methods recommended by ATSDR (2001a, 2001b). The derived values are listed in Table 46, which also lists the chronic oral MRLs or guidance values. BINWOEs have been developed for these endpoints also, as presented in Section 2.3, and summarized later in Section 3.

Table 46. MRLs and TTDs for Chronic Oral Exposure to Chemicals of Concern. See Appendices A, B, C, and D for Details of Derivations.

Endpoint	Chemical			
	Lead PbB µg/dL	Arsenic (mg/kg/day)	Cadmium (mg/kg/day)	Chromium(VI) (mg/kg/day)
Neurological	10[a]	$3x10^{-4}$	$2x10^{-4}$	$1x10^{-2}$
Dermal	NA	$3x10^{-4}$ (chronic MRL)	NA	NA
Renal	34	$9x10^{-2}$	$2x10^{-4}$ (chronic MRL)	$1x10^{-2}$
Cardiovascular	10	$3x10^{-4}$	$5x10^{-3}$	NA
Hematological	10	$6x10^{-4}$	$8x10^{-4}$	$3x10^{-3}$
Testicular	40	NA	$3x10^{-3}$	$5x10^{-3}$

[a]CDC PbB level of concern
NA = not applicable

The binary mixtures with the most extensive interaction databases are the lead-arsenic mixture and the lead-cadmium mixture. BINWOEs for relevant endpoints of concern for these mixtures are summarized in Tables 47 and 48. The predicted direction of interaction for the effects of these mixtures is not consistent across endpoints. This observation is most striking for the effects of cadmium on the toxicity of lead. The predicted direction is greater than additive for the neurological effects (the critical effect) and testicular effects (a less sensitive effect), less than additive for renal and hematological effects, and additive for cardiovascular effects.

Table 47. Summary of Endpoint-Specific BINWOEs for Lead and Arsenic		
	Lead on Arsenic	Arsenic on Lead
Endpoint	BINWOE Determinations	
Neurological	>IIIB (+0.23)	>IIB (+0.50)
Dermal	? (0)	NA
Renal	<IIIB (-0.23)	<IIIB (-0.23)
Cardiovascular	? (0)	? (0)
Hematological	<IIIB (-0.23)	<IIIB (-0.23)
Testicular	NA	? (0)

NA = not applicable

Table 48. Summary of Endpoint-Specific BINWOEs for Lead and Cadmium		
	Lead on Cadmium	Cadmium on Lead
Endpoint	BINWOE Determinations	
Neurological	? (0)	>IIIC (+0.1)
Renal	=IIAii (0)	<IIA (-0.71)
Cardiovascular	=IIIA (0)	=IIIA (0)
Hematological	=IIC (0)	<IIIB (-0.23)
Testicular	>IIA (+0.71)	>IIA (+0.71)

The observation of inconsistency in predicted direction of interaction underscores the uncertainty in extrapolating interactions from one endpoint to another. It also suggests the possibility that a less sensitive target organ may have the potential to impact a mixtures health assessment if it is affected synergistically. Concern would be heightened if several chemicals in the mixture affect that target organ, and if confidence in the interaction (as reflected by the BINWOE scores) is high.

BINWOE determinations for the critical effects of the mixture components—neurological (the critical effect of lead), dermal (the critical effect of arsenic), and renal (the critical effect of cadmium)—are summarized in Tables 49–51. Only five of the BINWOEs for neurological effects (Table 49) are non-zero scores: four of these are greater than additive. Confidence in the greater-than-additive

determinations is moderate (>IIB, +0.50) for the effect of arsenic on lead, low-moderate (>IIIB, +0.23) for the effect of lead on arsenic, and low (>IIIC, +0.10) for the effect of cadmium on lead and of chromium(VI) on arsenic. Confidence in the less-than-additive determination for the effect of arsenic on chromium(VI) is low (<IIIC2ii, -0.06). There are no data directly relevant to joint action on neurological endpoints for the other pairs of metals, and no clear mechanistic understanding. Therefore, the remaining BINWOEs are indeterminate with a score of 0.

Only one of the metals, arsenic, causes dermal effects following oral exposure. The BINWOEs for dermal effects (Table 50) are indeterminate (0) for the effect of lead or cadmium on arsenic toxicity, and greater than additive with low confidence (>IIIC, +0.10) for the effect of chromium(VI) on arsenic toxicity. BINWOEs are not applicable for effects on lead, cadmium, and chromium(VI) toxicity because these metals are not toxic to the skin by the oral route of exposure.

For renal toxicity (Table 51), BINWOEs are less than additive (with confidence ranging from low-moderate to high-moderate) for the effect of lead on arsenic (<IIIB, -0.23) for the effect of cadmium on lead (<IIA, -0.71), for the effects of arsenic on lead (<IIIB, -0.23) and chromium (<IIIB2iii, -0.14), and for the effect of chromium on arsenic (<IIIB2ii, -0.14). BINWOEs are additive (0) for the effects of lead on cadmium (=IIAii) and cadmium on arsenic (=IIB); confidence is moderate. Scores are indeterminate (0) for the remaining five BINWOEs.

Table 49. Matrix of BINWOE Determinations for Neurological Toxicity of Intermediate or Chronic Simultaneous Oral Exposure to Chemicals of Concern

		ON TOXICITY OF			
		Lead	Arsenic	Cadmium	Chromium(VI)
EFFECT OF	Lead		**>IIIB (+0.23)**	**? (0)**	? (0)
	Arsenic	**>IIB (+0.50)**		? (0)	**<IIIC2ii (-0.06)**
	Cadmium	**>IIIC (+0.10)**	? (0)		? (0)
	Chromium(VI)	? (0)	**>IIIC (=0.10)**	? (0)	

The BINWOE determinations shown in boldface type were explained in the tables in Section 2.3. As reviewed in Section 2.2, no pertinent interactions data were available for the remaining pairs of metals, and mechanistic information appeared inadequate or ambiguous, so indeterminate ratings are appropriate for these remaining pairs.

BINWOE scheme (with numerical weights in parentheses) condensed from ATSDR (2001a, 2001b):

DIRECTION: = additive (0); > greater than additive (+1): < less than additive (-1); ? indeterminate (0)

MECHANISTIC UNDERSTANDING:
I: direct and unambiguous mechanistic data to support direction of interaction (1.0);
II: mechanistic data on related compounds to infer mechanism(s) and likely direction (0.71);
III: mechanistic data do not clearly indicate direction of interaction (0.32).
TOXICOLOGIC SIGNIFICANCE:
A: direct demonstration of direction of interaction with toxicologically relevant endpoint (1.0);
B: toxicologic significance of interaction is inferred or has been demonstrated for related chemicals (0.71);
C: toxicologic significance of interaction is unclear (0.32).
MODIFYING FACTORS:
1: anticipated exposure duration and sequence (1.0);
2: different exposure duration or sequence (0.79);
a: *in vivo* data (1.0);
b: *in vitro* data (0.79);
i: anticipated route of exposure (1.0);
ii different route of exposure (0.79).

Table 50. Matrix of BINWOE Determinations for Dermal Toxicity of Intermediate or Chronic Simultaneous Oral Exposure to Chemicals of Concern

		ON TOXICITY OF			
		Lead	Arsenic	Cadmium	Chromium(VI)
EFFECT OF	Lead		**? (0)**	NA	NA
	Arsenic	NA		NA	NA
	Cadmium	NA	**? (0)**		NA
	Chromium(VI)	NA	**>IIIC (+0.10)**	NA	

The BINWOE determinations shown in boldface type were explained in the tables in Section 2.3. As reviewed in Section 2.2, no pertinent interactions data were available for the remaining pairs of metals, and mechanistic information appeared inadequate or ambiguous, so indeterminate ratings are appropriate for these remaining pairs.

BINWOE scheme (with numerical weights in parentheses) condensed from ATSDR (2001a, 2001b):

DIRECTION: = additive (0); > greater than additive (+1): < less than additive (-1); ? indeterminate (0)

MECHANISTIC UNDERSTANDING:
I: direct and unambiguous mechanistic data to support direction of interaction (1.0);
II: mechanistic data on related compounds to infer mechanism(s) and likely direction (0.71);
III: mechanistic data do not clearly indicate direction of interaction (0.32).
TOXICOLOGIC SIGNIFICANCE:
A: direct demonstration of direction of interaction with toxicologically relevant endpoint (1.0);
B: toxicologic significance of interaction is inferred or has been demonstrated for related chemicals (0.71);
C: toxicologic significance of interaction is unclear (0.32).
MODIFYING FACTORS:
1: anticipated exposure duration and sequence (1.0);
2: different exposure duration or sequence (0.79);
a: *in vivo* data (1.0);
b: *in vitro* data (0.79);
i: anticipated route of exposure (1.0);
ii different route of exposure (0.79).

Table 51. Matrix of BINWOE Determinations for Renal Toxicity of Intermediate or Chronic Simultaneous Oral Exposure to Chemicals of Concern

		ON TOXICITY OF			
		Lead	Arsenic	Cadmium	Chromium(VI)
EFFECT OF	Lead		**<IIIB (-0.23)**	**=IIAii (0)**	? (0)
	Arsenic	**<IIIB (-0.23)**		**? (0)**	**<IIIB2ii (-0.14)**
	Cadmium	**<IIA (-0.71)**	**=IIB (0)**		? (0)
	Chromium(VI)	? (0)	**<IIIB2ii (-0.14)**	? (0)	

The BINWOE determinations shown in boldface type were explained in the tables in Section 2.3. The remaining BINWOEs are marked NA = not applicable because oral exposure to this metal does not cause dermal effects.

BINWOE scheme (with numerical weights in parentheses) condensed from ATSDR (2001a, 2001b):

DIRECTION: = additive (0); > greater than additive (+1): < less than additive (-1); ? indeterminate (0)

MECHANISTIC UNDERSTANDING:
I: direct and unambiguous mechanistic data to support direction of interaction (1.0);
II: mechanistic data on related compounds to infer mechanism(s) and likely direction (0.71);
III: mechanistic data do not clearly indicate direction of interaction (0.32).
TOXICOLOGIC SIGNIFICANCE:
A: direct demonstration of direction of interaction with toxicologically relevant endpoint (1.0);
B: toxicologic significance of interaction is inferred or has been demonstrated for related chemicals (0.71);
C: toxicologic significance of interaction is unclear (0.32).
MODIFYING FACTORS:
1: anticipated exposure duration and sequence (1.0);
2: different exposure duration or sequence (0.79);
a: *in vivo* data (1.0);
b: *in vitro* data (0.79);
i: anticipated route of exposure (1.0);
ii: different route of exposure (0.79).

The remaining endpoints of concern are not the critical effects for any of the metals, but are relatively sensitive effects of one or more of these metals, are effects in common across two or more of the metals, or are known to be affected synergistically by another metal in the mixture. These are cardiovascular, hematological, and reproductive (testicular) effects. BINWOEs have been developed for these effects as well, and are summarized in Tables 52–54.

The BINWOE determinations for cardiovascular toxicity (Table 52) are additive for effects of lead on cadmium and vice versa (=IIIA, 0), and greater than additive (>IIIC, +0.10) for the effect of chromium(VI) on arsenic. Six BINWOEs are indeterminate (0), and three are not applicable (for effects on chromium(VI), which is not known to be a cardiovascular toxicant). Thus, all but one of the BINWOE scores are zero, and that score is close to zero.

Six of the BINWOE determinations for hematological toxicity (Table 53) are less than additive, with low-moderate confidence (<IIIB, -0.23). One BINWOE is greater than additive with low confidence (IIIC, +0.10), one BINWOE is additive (=IIC, 0), and the remaining four, for pairs involving chromium(VI), are indeterminate (0).

For testicular toxicity (Table 54), the two BINWOEs for the lead-cadmium mixture are greater than additive, with moderately high confidence (>IIA, +0.71), the BINWOEs for the effects of arsenic on cadmium and on chromium(VI) are less than additive, with low confidence (<IIIB2ii, -0.14, and <IIC2ii, -0.06), BINWOEs for an effect on arsenic are not applicable because arsenic is not known to have testicular effects, and the remaining five BINWOEs are indeterminate (0).

Estimation of hazard quotients for lead is problematic because of the lack of an oral MRL or RfD. The use of media-specific slope factors and site-specific environmental monitoring data has been recommended by ATSDR to predict media-specific contributions to blood lead (ATSDR 1999b). The predicted contributions from the individual media are summed to yield a total predicted PbB level. The media-specific slope factors were derived from regression analysis of lead concentrations in water, soil, dust, diet, or air and PbBs for various populations. In order to estimate a hazard quotient, the predicted PbB can be divided by the PbB of 10 µg/dL, the level of concern (CDC 1991). The development of TTDs for lead is based on PbB as well.

Table 52. Matrix of BINWOE Determinations for Cardiovascular Toxicity of Intermediate or Chronic Simultaneous Oral Exposure to Chemicals of Concern

		ON TOXICITY OF			
		Lead	Arsenic	Cadmium	Chromium(VI)
EFFECT OF	Lead		**? (0)**	**=IIIA (0)**	NA
	Arsenic	**? (0)**		? (0)	NA
	Cadmium	**=IIIA (0)**	? (0)		NA
	Chromium(VI)	? (0)	**>IIIC (+0.10)**	? (0)	

The BINWOE determinations shown in boldface type were explained in the tables in Section 2.3. As reviewed in Section 2.2, no pertinent interactions data were available for the remaining pairs of metals, and mechanistic information appeared inadequate or ambiguous, so indeterminate ratings are appropriate for these remaining pairs.

BINWOE scheme (with numerical weights in parentheses) condensed from ATSDR (2001a, 2001b):

DIRECTION: = additive (0); > greater than additive (+1): < less than additive (-1); ? indeterminate (0)

MECHANISTIC UNDERSTANDING:
I: direct and unambiguous mechanistic data to support direction of interaction (1.0);
II: mechanistic data on related compounds to infer mechanism(s) and likely direction (0.71);
III: mechanistic data do not clearly indicate direction of interaction (0.32).
TOXICOLOGIC SIGNIFICANCE:
A: direct demonstration of direction of interaction with toxicologically relevant endpoint (1.0);
B: toxicologic significance of interaction is inferred or has been demonstrated for related chemicals (0.71);
C: toxicologic significance of interaction is unclear (0.32).
MODIFYING FACTORS:
1: anticipated exposure duration and sequence (1.0);
2: different exposure duration or sequence (0.79);
a: *in vivo* data (1.0);
b: *in vitro* data (0.79);
i: anticipated route of exposure (1.0);
ii: different route of exposure (0.79).

Table 53. Matrix of BINWOE Determinations for Hematological Toxicity of Intermediate or Chronic Simultaneous Oral Exposure to Chemicals of Concern

		ON TOXICITY OF			
		Lead	Arsenic	Cadmium	Chromium(VI)
EFFECT OF	Lead		**<IIIB (-0.23)**	**=IIC (0)**	? (0)
	Arsenic	**<IIIB (-0.23)**		**<IIIB (-0.23)**	**<IIIC2ii (-0.06)**
	Cadmium	**<IIIB (-0.23)**	**<IIIB (-0.23)**		? (0)
	Chromium(VI)	? (0)	**>IIIC (+0.10)**	? (0)	

The BINWOE determinations shown in boldface type were explained in the tables in Section 2.3. As reviewed in Section 2.2, no pertinent interactions data were available for the remaining pairs of metals, and mechanistic information appeared inadequate or ambiguous, so indeterminate ratings are appropriate for these remaining pairs.

BINWOE scheme (with numerical weights in parentheses) condensed from ATSDR (2001a, 2001b):

DIRECTION: = additive (0); > greater than additive (+1): < less than additive (-1); ? indeterminate (0)

MECHANISTIC UNDERSTANDING:
I: direct and unambiguous mechanistic data to support direction of interaction (1.0);
II: mechanistic data on related compounds to infer mechanism(s) and likely direction (0.71);
III: mechanistic data do not clearly indicate direction of interaction (0.32).
TOXICOLOGIC SIGNIFICANCE:
A: direct demonstration of direction of interaction with toxicologically relevant endpoint (1.0);
B: toxicologic significance of interaction is inferred or has been demonstrated for related chemicals (0.71);
C: toxicologic significance of interaction is unclear (0.32).
MODIFYING FACTORS:
1: anticipated exposure duration and sequence (1.0);
2: different exposure duration or sequence (0.79);
a: *in vivo* data (1.0);
b: *in vitro* data (0.79);
i: anticipated route of exposure (1.0);
ii: different route of exposure (0.79).

Table 54. Matrix of BINWOE Determinations for Testicular Toxicity of Intermediate or Chronic Simultaneous Oral Exposure to Chemicals of Concern

		ON TOXICITY OF			
		Lead	Arsenic	Cadmium	Chromium(VI)
EFFECT OF	Lead		NA	**>IIA (+0.71)**	? (0)
	Arsenic	? (0)		**<IIIB2ii (-0.14)**	**<IIIC2ii (-0.06)**
	Cadmium	**>IIA (+0.71)**	NA		? (0)
	Chromium(VI)	? (0)	NA	? (0)	

The BINWOE determinations shown in boldface type were explained in the tables in Section 2.3. Arsenic is not known to have testicular effects, so BINWOEs for the testicular toxicity of arsenic are marked NA = not applicable. As reviewed in Section 2.2, no pertinent interactions data were available for the remaining pairs of metals, and mechanistic information appeared inadequate or ambiguous, so indeterminate ratings are appropriate for these remaining pairs.

BINWOE scheme (with numerical weights in parentheses) condensed from ATSDR (2001a, 2001b):

DIRECTION: = additive (0); > greater than additive (+1): < less than additive (-1); ? indeterminate (0)

MECHANISTIC UNDERSTANDING:
I: direct and unambiguous mechanistic data to support direction of interaction (1.0);
II: mechanistic data on related compounds to infer mechanism(s) and likely direction (0.71);
III: mechanistic data do not clearly indicate direction of interaction (0.32).
TOXICOLOGIC SIGNIFICANCE:
A: direct demonstration of direction of interaction with toxicologically relevant endpoint (1.0);
B: toxicologic significance of interaction is inferred or has been demonstrated for related chemicals (0.71);
C: toxicologic significance of interaction is unclear (0.32).
MODIFYING FACTORS:
1: anticipated exposure duration and sequence (1.0);
2: different exposure duration or sequence (0.79);
a: *in vivo* data (1.0);
b: *in vitro* data (0.79);
i: anticipated route of exposure (1.0);
ii: different route of exposure (0.79).

Oral MRLs have not been developed for chromium(VI), but health assessments often use the RfD (IRIS 2001). Alternatively, the upper end of the range of the estimated safe and adequate daily dietary intake of 200 µg Cr/kg/day (NRC 1989) has been adopted as provisional guidance for oral exposure to chromium(VI) and chromium(III) by ATSDR (2000b).

Proceeding with the TTD modification of the hazard index approach involves calculating endpoint-specific hazard indexes for each endpoint of concern, as described in ATSDR (2001a, Section 2.3.2 and Figure 2 with accompanying text). For example, a hazard index for neurological effects of this mixture is calculated as follows:

$$HI_{NEURO} = \frac{E_{Pb}}{CDC\ PbB_{Pb\ NEURO}} + \frac{E_{As}}{TTD_{As\ NEURO}} + \frac{E_{Cd}}{TTD_{Cd\ NEURO}} + \frac{E_{Cr(VI)}}{TTD_{Cr(VI)\ NEURO}}$$

where HI_{NEURO} is the hazard index for neurological toxicity, E_{Pb} is the exposure to lead (as predicted PbB in µg/dL), $CDC\ PbB_{NEURO}$ is the CDC PbB of concern (10 µg/dL) for the neurological toxicity of lead (ATSDR 1999b; CDC 1991), E_{As} is the exposure to arsenic (as the oral intake in the same units as the corresponding TTD, mg/kg/day), $TTD_{As\ NEURO}$ is the TTD for the neurological toxicity of arsenic, and so forth.

If one or more of the endpoint-specific hazard indexes exceed one, they provide preliminary evidence that the mixture may constitute a health hazard due to the joint toxic action of the components on that endpoint (ATSDR 2001a). The qualitative WOE method is then used to estimate the potential impact of interactions on the endpoint-specific hazard indexes (Figure 2, ATSDR 2001a), using the BINWOEs developed in this profile. As discussed in ATSDR (2001a), when the endpoint-specific hazard index is greater than unity and/or when the qualitative WOE indicates that joint toxic action may be greater than additive, further evaluation using methods described by ATSDR (1992) is needed.

Similarly, if the estimated cancer risk for arsenic equals or exceeds $1x10^{-4}$, this provides preliminary evidence of a health hazard (ATSDR 2001a). The qualitative WOE is then used to estimate the potential impact of interactions, but for arsenic carcinogenicity, the WOE does not significantly impact conclusions. Mechanistic considerations suggest that the effect of chromium(VI) on arsenic carcinogenicity may be greater than additive, but confidence in this assessment is low. The remaining BINWOEs for the effects of the mixture components on arsenic carcinogenicity are indeterminate.

Therefore, if the estimated cancer risk equals or exceeds $1x10^{-4}$, further evaluation using methods described by ATSDR (1992) is needed.